Chemical Models for Aqueous Biodynamical Processes

by Julio F. Mata-Segreda

Licenciado, Universidad de Costa Rica, 1971

Professor in Charge
Richard L. Schowen

Committee Members
Mailin D. Harmony
Siegfried Lindenbaum

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1975

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Submitted to the Department of Chemistry
and the Faculty of the Graduate School
of the University of Kansas in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy

[redacted] Dissertation Committee:

Richard L. Schowen
Chairman

Marlin D Hawley

Siegfried Lindenbaum

MAY 1975

This work is dedicated to the memory of my father, to my mother, and to my wife and son Julio.

Acknowledgements

When the time comes for writing a thesis, one begins to realize how fruitful it has been to be associated with Professor Schowen, or as we would say in our jargon: "He's quite a Sonny." For me, it has been an invaluable experience having spent these three years working for him. Although sometimes he almost made me crazy when he used the terrible sentence *you ought to be able to do it*, he also taught me not only that it could get done but also that I was really able to solve the problem. Perhaps this has been the best part of my learning from him.

To my wife Victoria, there are very many things I could say; but not even a thousand words could describe my appreciation and indebtness. To my son, who has been my everyday sunshine for the past 2½ years, I say I love you, Julito.

I also have to thank my Mother and my family for their continuous encouragement, as well as to my "grandparents" in the U.S., Bernard and Gladys Nicolay.

To the members of this group, sonnies Dan Quinn, Jim Elrod, Rich and Ruth Gandour, Mo Hegazi (who let me use some of his results before publication), Barbara Schowen, and Mary Haddican (who typed this thesis), as well as to John Hogg and K. S. Venkatasubban,who already overcame the graduate-school energy barrier. "It's been a real pleasure, Sonnies!"

I acknowledge the contribution to this thesis made by Stanley Wint, who measured the isotopic fractionation factors of the *gem*-diols and sugars (*vide infra*).

A very special debt of gratitude is owed to the People of Costa Rica who gave me the opportunity (through the University of Costa Rica) to work for one of the finest men in the isotope effect field.

I should also like to acknowledge the valuable help of Professors M. D. Harmony and S. Lindenbaum, who kindly read this thesis.

Financial support by the Universities of Costa Rica and Kansas, the Chemistry Department, the National Science Foundation and the National Institutes of Health is acknowledged.

Abstract

The proton inventory method was applied to the study of three processes: the viscous flow of water, the neutral hydrolysis of esters, and the exchange reaction between aqueous sodium ion and the carboxylic exchanger *Amberlite CG-50®*.

The fluidity (1/viscosity) of mixtures of protium and deuterium oxides at 298.16 K can be described by the equation $\Phi_n = \Phi_o(1 - n + 0.90n)^2$. This result indicates that two protons contribute equally to the overall isotope effect. The proposed mechanism for momentum transfer involves an interstitial water molecule linked to "flowing" molecular sheaths.

The rate constants of neutral hydrolysis of ethyl trifluoroacetate at 298.16 K can be described by the equation $k_n = k_o(1-n+0.47n)(1-n+0.78n)^2$. This result suggests a catalytic entity with 67% hydronium ion character which we have called the *paene*-hydronium ion.

The rate of exchange of the reaction $Na(aq)^+$ + *Amberlite CG-50®* was found to be independent of a) $[Na^+]$/(resin); b) hydrodynamic conditions; c) nature of cation (Li^+, Na^+, K^+). The solvent isotope effect for Na and K exchange was found to be 3.06 ± 0.17 and 3.31 ± 0.38, respectively. These results suggest that diffusion of the newly exchanged hydronium ion through the polymeric matrix is rate determining. The reaction rate constants for sodium exchange in mixtures of H_2O-D_2O at 298.16 K can be described by the equation $k_n = k_o(1 - n + 0.70n)^3$ which supports the proposed mechanism.

Fractionation factors were measured for four geminal hydroxylic compounds as models for the tetrahedral intermediate in the hydrolysis

of carboxylic acid derivatives. The values are 1.23 ± 0.08 for chloral hydrate; 1.24 ± 0.20 for ninhydrin; 1.28 ± 0.17 for D-glucose; and 1.23 ± 0.02 for D-fructose. These values indicate that hydrogens are more tightly bound in these molecules than in bulk water. A theoretical calculation of deuterium isotope effects was made on a *gem*-diol model. The isotope effect K_D/K_H increases with an increase in the hydroxylic torsional force constant. An extensive table of isotopic fractionation factors is given.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Introduction

The first question the reader might ask himself is: why the study of models for biodynamical processes? The reason to study biological processes is intuitively obvious: any effort made towards the benefit of mankind is intrinsically noble.[1] But the point to be discussed in this section is the reason for studying models instead of the actual systems, specifically enzymic systems.

In many cases, the structural details of these catalysts are not known; therefore, more progress can be made by studying suitable model systems.

A chemical model study can be one in which the behavior of the system of interest is imitated by other chemical species,[2] or it can be a study in which the real system interacts with non-natural probes.[3]

In this work, we shall use a third kind of model study, in which the system of interest is imitated and is also studied by using non-natural probes.

In our case, this non-natural probe is the use of isotopes in the study of a model system. For example, the study of the ion exchange process in a carboxylic acid type resin (*vide infra*) intends to find how the exchanger works, and the result is compared later with results obtained from the study of metal-ion binding processes of metalloenzymes.

The four main topics in this thesis are:

1. The mechanism of water viscous flow.
2. Neutral hydrolysis of esters.
3. Fractionation factors of *gem*-diols and related compounds.
4. Mechanism of ion exchange in crosslinked carboxylic polymers.

The studies in (1) and (4) contribute to the solution of basic problems in chemical physics, which at the same time are of utmost importance for the problem of osmotic transport in living systems.

The second study is of basic value to organic chemistry, but at the same time is tremendously relevant to the problem of enzyme-catalyzed ester hydrolysis. *Gem*-diols and related compounds were studied since they are good models for the tetrahedral intermediate in the hydrolysis of carboxylic acid derivatives.

As can be seen, a whole new intermediate discipline has been created in the past ten years[4] that scientists have agreed to call "Bioorganic Chemistry."

Although the primary interests of the writer are not bioorganic chemical ones, he feels a sort of joy when he looks at a body of work collected with the primary noble purpose of benefiting directly *all* mankind.

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CHAPTER I

THE PROTON INVENTORY TECHNIQUE

Introduction. Since many of the problems described in this thesis were studied by applying the *Proton Inventory Technique**, we decided that a section devoted to its nature was necessary. As the name suggests, the method consists of taking an inventory of those protons whose dynamics are relevant to the reaction pathway. At this point it is necessary to define what we mean by dynamics and reaction pathway. Reaction pathway, or strictly *average reaction pathway* is generally the minimum energy trajectory on the potential surface, from reactants to products. Movement along this minimum energy trajectory is generally described by the *reaction coordinate*, a quantity that measures the distance the molecular system has traveled along the pathway.[1] We define dynamics as the motion of atoms in a molecule and the action of forces in producing a chemical change (structural change). Furthermore, we should like to use the word *kinetics* to imply exclusively the dynamics of the reacting system at a particular point on the reaction pathway.[34] From the theory of kinetic isotope effects[2] we know that the origin of isotope-effect phenomena lies in the kinetics of the transition state and in the kinetics of the reactant state. If k is the reaction rate constant for the reaction of the more lightly substituted system and k' the corresponding quantity for the more heavily substituted one, we have that:

$$\frac{k}{k'} = \frac{\text{Transition-state kinetic contribution}}{\text{Reactant-state kinetic contribution}} \qquad (1)$$

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*This method was baptized the *Proton Inventory Technique* by Professor Richard L. Schowen, although the method itself was applied before he started the first grade back in the hills.

These contributions are formally stated in terms of the corresponding isotopic ratio of partition functions for the transition state and reactant state, respectively. The following is an outline of the theoretical background necessary for the development of the theory of the Proton Inventory Technique.

*The Theory of Absolute Reaction Rates--An Outline.** This theory treats chemical reactions in such a way that the reacting species form an activated complex which is said to be "in the transition state" and which is situated at the top of an energy barrier lying between the initial state (reactants) and final state (products). It is also assumed that the reaction rate is determined by the frequency with which the complex travels over the top of the barrier. This type of formulation of chemical processes seems first to have been proposed by Marcelin,[3] who considered the reacting species to cross a "critical surface in phase space." A more general approach to rate processes has been given by Keck,[4] and recently Koeppl[5] has dealt with the particular boundary conditions on Keck's general theory which produce Absolute Rate Theory. The formulation of transition state theory was made by Eyring.[6] A simplified development of the basic equation is given below.[7] Consider the following hypothetical reaction:

$$A + B + \ldots \rightleftharpoons [\neq] \longrightarrow \text{products}$$

It will be assumed that *the reactants are in thermal equilibrium with the activated complexes.* It is also necessary to assure that the

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*For a complete treatment see references 6 and 7.

complexes decompose at a finite rate. One can suppose that the degree of freedom associated with the mode of decomposition of the activated complex can be thought to be a very low frequency vibration (very large amplitude). Since every time this "vibration" occurs products are formed, the rate of the reaction is equal to:

$$\text{rate} = \nu_L [\neq] \tag{2}$$

where ν_L is the frequency of this critical mode. The theory assumes the existence of an equilibrium condition between the reactants and activated states, so an equilibrium constant should exist and define the system. If we consider the case where the system behaves ideally, the equilibrium constant becomes a concentration equilibrium constant and can be expressed in terms of the corresponding partition functions[8]:

$$K^* = \frac{Q^*}{\pi Q_R} \tag{3}$$

It is assumed that the complete partition function of the activated complex species, Q^*, can be separated into the partition function corresponding to the decomposition mode and a new *defective* partition function, $Q^{\neq}$, such that:

$$Q^* = q_L Q^* \tag{4}$$

If the critical mode is assumed to be a low frequency harmonic oscillation, the value of q_L is approximately $KT/h\nu_L$, and the expression for the rate constant becomes:

$$k = \frac{KT}{h} \frac{Q^{\neq}}{\pi Q_R} \tag{5}$$

or as it is usually written

$$k = \frac{KT}{h} K^{\neq} \tag{6}$$

where $K^{\neq}$ is the so-called *defective* equilibrium constant. No comment will be made on the transmission coefficient, and it will be assumed to have a value of 1.0.

Comments on the Nature of $K^{\neq}$. To our knowledge, Kreevoy[9] has been the only one who has been concerned with the defectiveness of $K^{\neq}$, although no definite conclusions have been given. $K^{\neq}$ is defective because $Q^{\neq}$ is missing one degree of freedom. Since not every degree of freedom contributes to the average energy or heat capacity of a system,[10] it is interesting to find the contribution from the decomposition mode in a polyatomic system. Since the critical frequency was postulated to be very low, the energy contribution from this degree of freedom to the energy content of the transition state and to the energy of activation must be very small. The derived thermodynamic quantities $\Delta G^{\neq}$, $\Delta H^{\neq}$, $\Delta S^{\neq}$, and $\Delta C_p^{\neq}$ are also defective, since they do not have any contribution from the critical mode. Nevertheless, the qualitative picture obtained from these functions must not be different from that given by the exact functions. In qualitative terms, we can say that since q_L has only the critical kinetic information in itself, this makes it not "relevant" to the equilibrium condition, that is, the critical mode has no unstable counterpart in the reactant state, therefore it is not relevant to the equilibration of "forces." This statement is our personal corollary from the principle of microscopic reversibility.[7b]

The Nature of the Proton Inventory Technique. In this method, rate (or equilibrium) constants are measured in mixtures of isotopic hydroxylic solvents, and the mathematical relation between rate and solvent isotopic composition is obtained and examined for mechanistic information. The theory of equilibrium and rate processes in mixtures of light and heavy water has been presented by Gross and Butler and further extended by other authors.[11] A more general source of information is a recent handbook compiled by the Bioorganic Chemical Dynamics Group at the University of Kansas.[12] Observed solvent isotope effects are the result of exchange and medium or transfer processes. In the first part of this section, we shall deal with the exchange effect and then, a more general approach will be discussed.

The approach given here is philosophically different from that traditionally taken.[11] Several authors use the ratio $K_n^{\neq}/K_o^{\neq}$ to be equal to the partial solvent isotope effect k_n/k_o. That assumption is fair but dangerous. Before going further, an important concept will have to be discussed: the isotopic fractionation factor.

a) *Isotopic Fractionation Factor.* This parameter measures the preference for deuterium relative to protium of the i-th hydrogenic site, compared to the same preference in the bulk of the solvent. For example, for a substrate BL_N (L = H,D) one has

$$\phi_i = \frac{[BL_{N-1}D]/[BL_{N-1}H]}{n/(1-n)} \qquad (7)$$

where n is the deuterium mole fraction in the solvent. It is assumed that the deuterium preference of the i-th hydrogenic site is independent

of whether the other N - 1 sites are occupied by protium or deuterium. Further, it is assumed that all sites of the same kind have equal deuterium preferences in all isotopic configurations of BL_N. This is known as the rule of the geometric mean.[13] The rule is not entirely correct. For example, the equilibrium constant for the exchange reaction

$$H_2O + D_2O = 2HDO$$

can be predicted to be 4. The value obtained experimentally and by statistical mechanical procedures using water-species vibrational frequencies is about 3.8,[13-15] which is only about 6% different from the predicted value of 4. The error introduced by this rule is small enough to introduce any severe errors in the method of the *proton inventory*.[14-15]

b) *An Example*. Let us suppose a compound RH_2 with two identical exchangeable sites. RH_2 is transformed into products *via* a transition state $(TH_2)^{\neq}$ at a rate $v_o = k_o[RH_2]$. When the same reaction is carried out in D_2O, one shall observe the reaction rate to be $v_2 = k_2[RD_2]$. Further experiments in H_2O-D_2O mixtures (L_2O) can be carried out and the observed rate will be the sum of the previous two and of the hemiexchanged species RHD. The following equations can be written to describe the system:

$$RH_2 \longrightarrow (TH_2)^{\neq} \longrightarrow \text{products} \qquad (8a)$$

$$RHD \longrightarrow (THD)^{\neq} \longrightarrow \text{products} \qquad (8b)$$

$$RD_2 \longrightarrow (TD_2) \longrightarrow \text{products} \qquad (8c)$$

According to the rule of the geometric mean,[13] one can assume that RHD and RDH behave the same way and therefore the observed reaction rate can be described by the following equations:

$$v_n = v_o + 2v_1 + v_2 \tag{9a}$$

$$k_n[RL_2] = k_o[RH_2] + 2k_1[RHD] + k_2[RD_2] \tag{9b}$$

It is obvious that the amount of RH_2, RHD, and RD_2 will vary continuously with the deuterium atom fraction of the solvent and so will the overall reaction rate. In order to discover the mathematical dependence of the concentration of the three species with n, one can work out the relation between $[RL_2]$ with n and the respective fractionation factors. Equation 9b can be rearranged to

$$\frac{k_n[RL_2]}{k_o[RH_2]} = 1 + 2\frac{k_1[RHD]}{k_o[RH_2]} + \frac{k_2[RD_2]}{k_o[RH_2]} \tag{10}$$

From the definition of isotopic fractionation factor we have that

$$[RHD]/[RH_2] = \phi_R \frac{n}{(1-n)} \tag{11}$$

$$[RD_2]/[RH_2] = \phi_R^2 \frac{n^2}{(1-n)^2} \tag{11b}$$

where ϕ_R is the isotopic fractionation factor of any of the hydrogenic positions of RL_2. Equation 10 can now be written

$$k_n[RL_2]/k_o[RH_2] = 1 + 2\frac{k_1}{k_o}\phi_R\frac{n}{(1-n)} + \frac{k_2}{k_o}\phi_R^2\frac{n^2}{(1-n)^2} \tag{12}$$

The ratio of the reaction rate constants can be obtained in terms of

ϕ_R easily. According to Eyring's theory

$$k_1/k_o = \exp -[(\delta_I G^{\neq} - \delta_I G°)/RT] \tag{13}$$

By adding and subtracting the isotope effect on the free energy of the solvent species, the reader can easily verify that

$$k_1/k_o = \phi^*/\phi_R \tag{14}$$

where ϕ^* is the *defective* fractionation factor of the transition state. ϕ^* is defective because the free energy of the transition state is defined to be a defective function (see page 4). By the same token and using the rule of the geometric mean, one obtains that

$$k_2/k_o = (\phi^*/\phi_R)^2 \tag{15}$$

Thus, equation 12 can now be written as

$$k_n[RL_2]/k_o[RH_2] = (1 - n + n\phi^*)^2 \tag{16}$$

The left-hand side of equation 16 can be easily transformed into $k_n(1 - n + n\phi_R)^2/k_o$ and equation 16 transformed into

$$\frac{k_n}{k_o} = \frac{(1 - n + n\phi^*)^2}{(1 - n + n\phi_R)^2} \tag{17}$$

One can see that there will be a $(1 - n + n\phi)$ term for every exchangeable site in the reactants and transition state. The general equation can be written as follows:

$$\frac{k_n}{k_o} = \frac{\prod (1 - n + n\phi_i^*)}{\prod (1 - n + n\phi_R)} \tag{18}$$

where the products are taken over the hydrogenic sites in the transition state and reactants, respectively.

From the experimental result, an inventory is taken to find how many protons contribute to the observed solvent isotope effect, and the contribution of each one. Equation 18 is a more detailed version of equation 1. The transition-state and reactant-state kinetic contributions to k_n/k_o contain information such as force constants, bond lengths, etc. Specifically, this kind of information is contained in the different ϕ values. A more extensive account of the nature of isotopic fractionation factors can be found in Chapter IV.

Up to now, in the approach taken here we did not include any medium effects which along with the occurrence of exchange equilibria *may* contribute significantly to the observed solvent isotope effect. Since transfer effects are most of the time very small,[17-19,22-26] we feel that as a first approximation the approach given above is valid. The issue has created two schools of thought; one of them has taken a pessimistic viewpoint[20] and predicates that since transfer effects are not accounted for in the theory, therefore this type of experiments has no mechanistic value. We shall take the point of view of the other school and discuss the transfer problem.

Based on the conclusions (and equations) arrived at in earlier parts of this chapter, we can say that the free energy of activation for experiments of this sort can be expressed as follows:

$$k_n/k_o = \exp -(\delta_n \Delta G^{\neq}_{exch} + \delta_n \Delta G^{\neq}_{tr})/RT \qquad (19)$$

or

$$k_n/k_o = \frac{\prod(1 - n + n\phi_i^*)}{\prod(1 - n + n\phi_R)} \exp -(\delta_n \Delta G^{\neq}_{tr})/RT \qquad (19b)$$

The isotope effect on the free energy of transfer can be calculated in terms of the transfer activity coefficients of the transition state and reactant state.[21] Consider the transfer of, say, the reactants from one infinitely diluted aqueous solution to another infinitely diluted solution in a mixture L_2O, that is, any effects due to differences in the γ's have been eliminated.* The isotope effect on the free energy of transfer is given by the following equation:

$$\delta_n \Delta G^{\circ}_{tr} = RT \ln y_n \tag{20}$$

where y_n is the transfer activity coefficient. Consider liquid water to be a mixture of several water species (w_R) of mole fraction χ_R and fractionation factor ϕ^s_R, such that

$$\sum \chi_R \phi^s_R = 1.0 \tag{21}$$

When a solute is dissolved in L_2O, it perturbs the proportions of the water species (and might even create new ones). This can be written as a chemical reaction

$$S(g) \longrightarrow S_{(L_2O)} + \sum \frac{\Delta_R}{2} W^n_R$$

where $\Delta_R/2$ is obviously the algebraic increase in the number of W_R molecules produced as a result of dissolving one mole of the solute S. Thus, the transfer "reaction" can be written as follows:

$$S_{(H_2O)} + \sum \frac{\Delta_R}{2} W^n_R \longleftrightarrow S_{(L_2O)} + \sum \frac{\Delta_R}{2} W^{\circ}_R$$

where W°_R are now the several species in protium oxide. The following

mathematical relation can be obtained from the above equilibrium expression:

$$y_n^R = \frac{\prod [W_R^\circ]^{\Delta_R/2}}{\prod [W_R^n]^{\Delta_R/2}} \qquad (22)$$

If one assumes that the total number of water molecules per unit volume does not change (which is nearly true) the above equation can be written in terms of the corresponding water-species fractionation factors and n, as was done for the exchange effect in an earlier part of this section (*vide supra*). The result is given in equation 23:

$$y_n^R = \prod (1 - n + n\phi_R^s)^{-\Delta_R} \qquad (23)$$

Equation 19b can now be written as follows:

$$k_n/k_o = \frac{\prod (1 - n + n\phi_i^*)}{\prod (1 - n + n\phi_R)} \times \frac{\prod (1 - n + n\phi_R^s)^{-\Delta_R}}{\prod (1 - n + n\phi_i^s)^{-\Delta_i}} \qquad (24)$$

where, as before, the subscript R refers to reactants and i to the transition state. When the fractionation factors of the solvent molecules in the reactant and transition state are not very much different from each other, it is easy to see how equation 24 transforms into equation 18. As Gold points out,[21] this refinement is of no immediate assistance in a practical sense, since the values of Δ's and ϕ^s's are not available yet. The problem of the separation of exchange and transfer effects is by no means generally solved at present, but cases have been studied.[21,27,28] A significant breakthrough in the theory of solvent isotope effects has been the results of Salomaa and Mattsen in their attempt to verify equation 23.[29] They found a linear relation

between the free energy of solution of various solutes and the isotopic composition of L_2O mixtures. This linearity of the ΔG_s° values *vs* n plots provides clear support for Gold's theoretical formulation for the transfer activity coefficient of solutes in L_2O mixtures.

The isotopic fractionation factors of the solvation spheres of methoxide ion in methanol[30,31] and of ethoxide ion in ethanol[32] have been determined. Also, it was found that the solvation sphere of cyanide ion in methanol[33] does not discriminate either deuterium or protium.

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CHAPTER II

THE MECHANISM OF WATER VISCOUS FLOW

The Liquid State. This section presents exclusively the information necessary to understand the results from which an attempt is made to explain the mechanism of viscous flow of water. References 1 through 6 and various specialized articles in reference 7 are recommended for a more complete information on the subject of the liquid state and liquid solutions.

The Structure of Liquids. Liquids represent a peculiar compromise between order and disorder.[8] The cohesive forces in a liquid are strong enough to maintain a condensed state, but not sufficiently strong to avoid the translation of individual molecules. Liquids are classified from a chemical point of view, according to the types of cohesive forces that hold them together. There are ionic liquids such as molten salts, metallic liquids which are composed of ions and mobile electrons, associated liquids like water in which molecules are held together by means of hydrogen bonds, and finally molecular liquids in which cohesion is due to van der Waals forces among molecules.

Without even knowing the nature of the cohesive forces, one can obtain an estimate of their magnitude. This estimate is provided by the internal pressure of the liquid system, p_i, which is the thermodynamic quantity defined as follows:

$$p_i = (\partial E/\partial V)_T = T(\partial p/\partial T)_V - p \qquad (1)$$

where all terms in equation 1 have their usual meaning. The internal pressure indicates the work necessary to perform an isothermal expansion in a system, thus indicating the magnitude of the cohesive forces. The

relation between internal pressure and liquid structure can also be considered from the point of view of entropy, since $(\partial p/\partial T)_V = (\partial S/\partial V)_T$. For example, *iso*-propyl alcohol, which is an associated liquid, has a lower value of p_i than acetone.[9] To explain this, a comparison is made between the structures of liquid *iso*-propanol and acetone, a liquid in which only van der Waals forces operate. The structure of liquid acetone is "looser" than that of liquid *iso*-propanol. In this last liquid, a large part of its cohesive energy resides in the hydrogen bonds, which are broken when the liquid evaporates. In a small isothermal expansion, the hydrogen bonds will remain intact, the volume change occurs mostly by the increase in the spacing of the hydrocarbon portions of the molecules.[9] Persistence of the hydrogen-bonded structure in *iso*-propanol during the small isothermal expansion limits greatly the increase in disorder relative to the same process in acetone and leads to a lower value of $(\partial S/\partial V)_T$ of *iso*-propanol relative to acetone. By definition, the internal pressure of an ideal gas is zero, since no intermolecular forces occur, for an imperfect gas p_i becomes appreciable and in the case of a liquid it may become much greater than the external pressure. Liquids have been defined as modified gases[3a] due to the fact that their mechanical behavior is similar to that of gases. Also, liquids can be regarded as modified solids[3a,10] that are made of molecules packed in such a way that one of their nearest neighbors has been removed. This leaves the material with the right amount of volume expansion and a reasonable degree of short-range order. This idea can also be put in terms of "holes" traveling through closely packed molecules compared to

a gas in which molecules travel through space. This model due to Eyring[10] will be very useful for the discussion of the viscous flow process.

The Structure of Liquid Water. Since we shall adopt the Frank-Wen "flickering-cluster" model[11] for the structure of liquid water, it will be described briefly here. For a partial historical account of theoretical studies on liquid water see references 11 and 12,and for the most complete information available now see references 13 and 14, as well as the papers of Scheraga and co-workers in the *Journal of Physical Chemistry* from 1973 to 1974.

Water is a peculiar liquid due to many of its physical properties (melting point, boiling point, heat capacity, etc.) which are not characteristic of a sixth-group hydride. Upon melting, water contracts to a liquid denser than ice. Thermal expansion overweighs this contraction and the particular temperature of maximum density appears at 277.14 K. Spectroscopic and diffraction studies[3] show a high degree of three-dimensional structure clearly indicating strong intermolecular interactions. Diffraction experiments show that much of the tetrahedral structure found in ordinary low-pressure ice is still present in the liquid after melting.

In the Frank-Wen model, liquid water is considered to be made up of a variety of small polymeric species (clusters) in rapid equilibrium with each other and with monomeric water. The clusters are held together by hydrogen bonds. The system can be disturbed by the application of pressure, temperature and addition of solutes. Proton transfer processes are very rapid in water, so these transient clusters are made and broken

with average life times of less than 10^{-10} sec.[11]

Light water is less structured than its deuterated homolog at temperatures below 0 and 35°. This difference in the degree of structureness can be seen in the relative value of their viscosities. Heavy water has a greater temperature coefficient of viscosity than light water. This indicates that deuterium oxide structure breaks down faster as temperature rises than does that of protium oxide.[11] The larger structureness of heavy water relative to light water is also shown by the value of their internal pressures, 1693 atm and 1415 atm for H_2O and D_2O, respectively. The same conclusion could be obtained from the infrared studies of Bonner and Woolsey[15] and Bonner.[16]

The Viscous Flow Process. There is a general group of processes, the transport processes, in which some physical quantity such as mass, heat, momentum or electrical charge is transported from one region of the system to another. A simple approach, which does not pretend to be a formal mathematical treatment, is given here. Figure II-1 shows two regions of a system (R_1 and R_2) with a reference coördinate system.

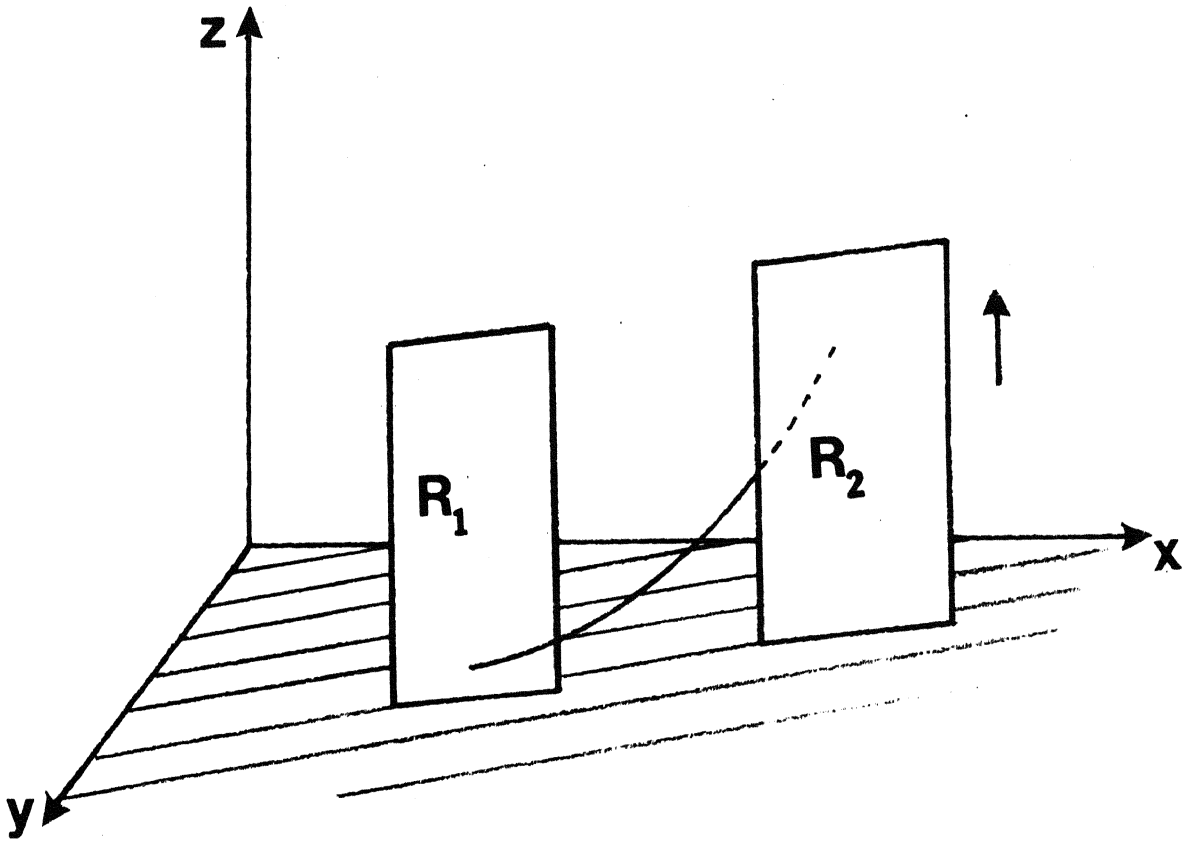
If heat is being transported from R_1 to R_2, Fourier's equation gives the flux of heat J_q between unit planes in R_1 and R_2 as follows:

$$J_q = -\lambda(\partial T/\partial X) \qquad (2)$$

where the proportionality constant λ is called the *thermal conductivity* of the system. When mass (chemical potential, that is, the free energy per mole of diffusing species) or electrical charge are being transported, Fick's and Ohm's laws, respectively, discribe the flux of the physical quantity, according to equations 3 and 4.

FIGURE II-1

TRANSPORT OF MOMENTUM


z
x
y
R_1
R_2

$$J_m = -D(\partial\mu/\partial X) \tag{3}$$

$$J_c = -K(\partial V/\partial X) \tag{4}$$

where D is the *diffusivity* of the moving species, K the *electrical conductivity* of the system and V the electrical potential between R_1 and R_2. As can be seen, the flux of a physical quantity is proportional to the negative gradient of a potential. This gradient is therefore a force, the driving force which determines the extent of transport.

If the plane at R_1 is fixed and the one at R_2 is moving in the z direction, a velocity gradient is established if R_1 and R_2 are "connected" somehow. This velocity gradient implicitly generates a momentum gradient. According to the ideas above, this momentum gradient should be the "driving force" for the transfer of momentum, and Newton's law of viscosity results immediately:

$$J_{mv} = -\eta(\partial v_z/\partial X) \tag{5}$$

where η is the viscosity of the system. In short, viscosity is a measure of internal friction among flowing molecular layers. For a complete macroscopic treatment of this phenomenon see references 17 and 18. The viscous flow process can now be discussed at a molecular level.[10]

Suppose a molecular layer is moving with respect to another one under the influence of an applied force. This process is assumed to involve the passage of a molecule from one equilibrium position to another in the same layer. In order for this "flowing" molecule to

jump, a hole must be available. The production of this void site needs the expenditure of of energy since work must be done against the intermolecular forces in the layer. The jump of the traveling molecule from one equilibrium position to the other may thus be seen as the passage of the system over a potential-energy barrier. Since the flow of a liquid is a rate process, Eyring[10] applied the formalism of Absolute Reaction Rate Theory to this phenomenon and obtained the following relation for the viscosity of a liquid:

$$\eta = \frac{hN}{V} \exp(\Delta G^{\neq}/RT) \qquad (6)$$

where h is Planck's constant, N Avogadro's number, V the molar volume of the liquid and $\Delta G^{\neq}$ the activation free energy for viscous flow. If $\Delta S^{\neq}$ is taken as a constant, equation 6 can be written as follows:

$$\eta = (hN/Ve^{-\Delta S^{\neq}/R}) e^{\Delta H^{\neq}/RT} \qquad (7a)$$

$$\eta = A \exp(\Delta H^{\neq}/RT) \qquad (7b)$$

A relationship like 7b had been previously suggested on empirical grounds by de Guzmán.[19]

To conclude this introduction an additional comment must be made on the properties of the activation thermodynamic parameters. For a molecule to flow, a hole must exist in the liquid. The energy necessary to make a hole of full molecular size in the bulk of a liquid system is equal to ΔE_{vap}, the energy of vaporization of the liquid. Since the hole must not necessarily be of full molecular size, as a first approximation the free energy of activation for viscous flow is expected to be

a fraction of the above mentioned vaporization energy. It has been found that many liquids obey the relation $\Delta G^{\neq} = 0.41\Delta E_{vap}$,[10] excluding metals but including alcohols. Since the free energy of activation values of alcohols can be correlated with their corresponding ΔE_{vap} values along with molecular liquids, cooperative effects between $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are suggested in alcohols and very probably in water also.

Statement of the Problem. This work examines the existing dynamic data for the viscous flow of water, in order to attempt to give a mechanism for water viscous flow, that is, the mechanism of momentum transfer in liquid water. The thermodynamic activation parameters will be examined and the *proton inventory* technique will be applied to this physical process.

RESULTS

The pressure dependence of the viscosity of liquid water has been studied extensively.[20,33] The viscosity of liquids varies with pressure according to equation 8:

$$(\partial \ln \eta/\partial p)_T = \Delta V^{\neq}/RT \qquad (8)$$

At temperatures below 306° K, the volume of activation ($\Delta V^{\neq}$) has been found to be negative, and then rises at higher pressures. An explanation of the structural significance of the sign of $\Delta V^{\neq}$ is given in the review article of Kell.[20] The negative volume of activation can be explained in terms of a four-coördinate flexible matrix in which the valence angles are almost tetrahedral. In such a situation, a net deformation of coördination bonds is needed to allow a molecule to commence its diffusive motion, and this deformation produces a decrease in volume.

According to the Einstein-Stokes equation for the diffusion of a Brownian spherical particle of radius r through a continuum, the processes of self-diffusion and viscous flow are inversely related as shown by equation 9:

$$D = KT/6\pi\eta r \qquad (9)$$

At 298 K, D for H_2O is 2.5 x 10^{-5} cm^2sec^{-1} and for D_2O 2.0 x 10^{-5} cm^2sec^{-1}.[20] The deuterium isotope effect on D is approximately equal to the ratio of the viscosities (1.23). According to equation 9, the diffusing species is the same size in H_2O and D_2O. Light and heavy waters are Einstein-Stokes liquids.

An Arrhenius plot of water viscosity and a plot of $\ln(\eta V)$ *vs* $1/T$ are not linear, as can be seen in Figures II-2 and II-3. This indicates that neither $\Delta H^{\neq}$ or $\Delta S^{\neq}$ nor both are constant. The enthalpy of activation can be obtained from the following relation:

$$\frac{\partial}{\partial(1/T)}\left[\ln(\eta V)\right]_p = \Delta H^{\neq}/R \qquad (10)$$

The $\ln(\eta V)$ - $1/T$ data obtained from the literature[21] were fitted to a polynomion in $(1/T)$[22] and the following result obtained:

TABLE II-1. Analysis of Variance for an Eyring-Set of Data on Water Viscosity[23]

	F-Value	F calc (%)
Linear Term	1603	22.9 (99.9)
Quadratic Term	655	25.4 (99.9)
Cubic Term	9	5.6 (95.0)

Since the viscosity measurements have not more than 1% error, the quadratic fit must represent the data satisfactorily:

$$\ln(\eta V) = -2.28 - (1749 \pm 129)/T + (561656 \pm 20833)/T^2 \qquad (11)$$

The enthalpy of activation is given by:

$$\Delta H^{\neq}/R = -(1749 \pm 129) + (1123312 \pm 41666)/T \qquad (12)$$

According to the above empirical function, the values of $\Delta H^{\neq}$ can be obtained with an error of ± 9%. From equation 12, the heat capacity of activation can be obtained, $\Delta C_p^{\neq} = (\partial \Delta H^{\neq}/\partial T)_p$, and at 298 K a value of

FIGURE II-2

ARRHENIUS PLOT OF WATER VISCOSITY

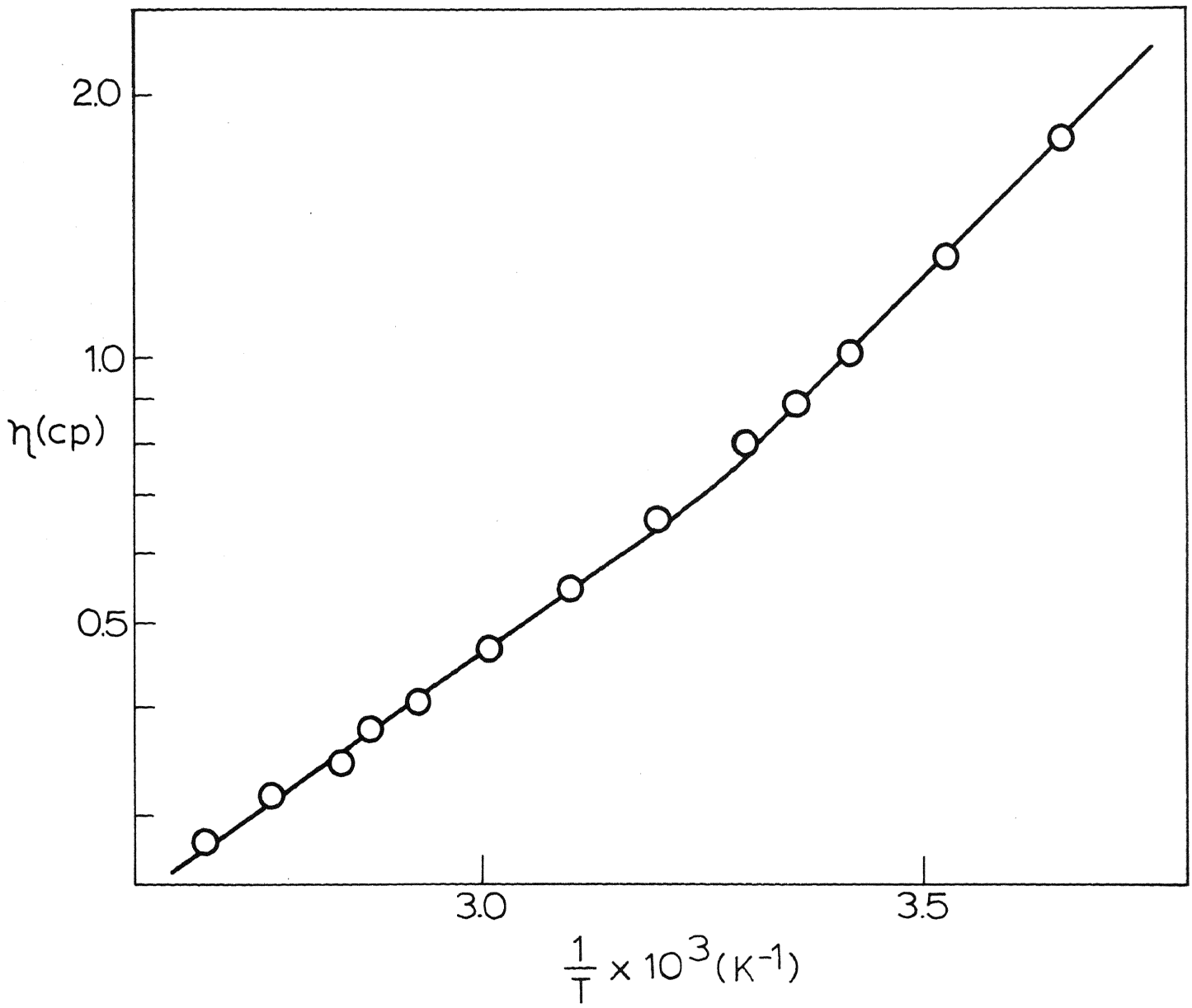
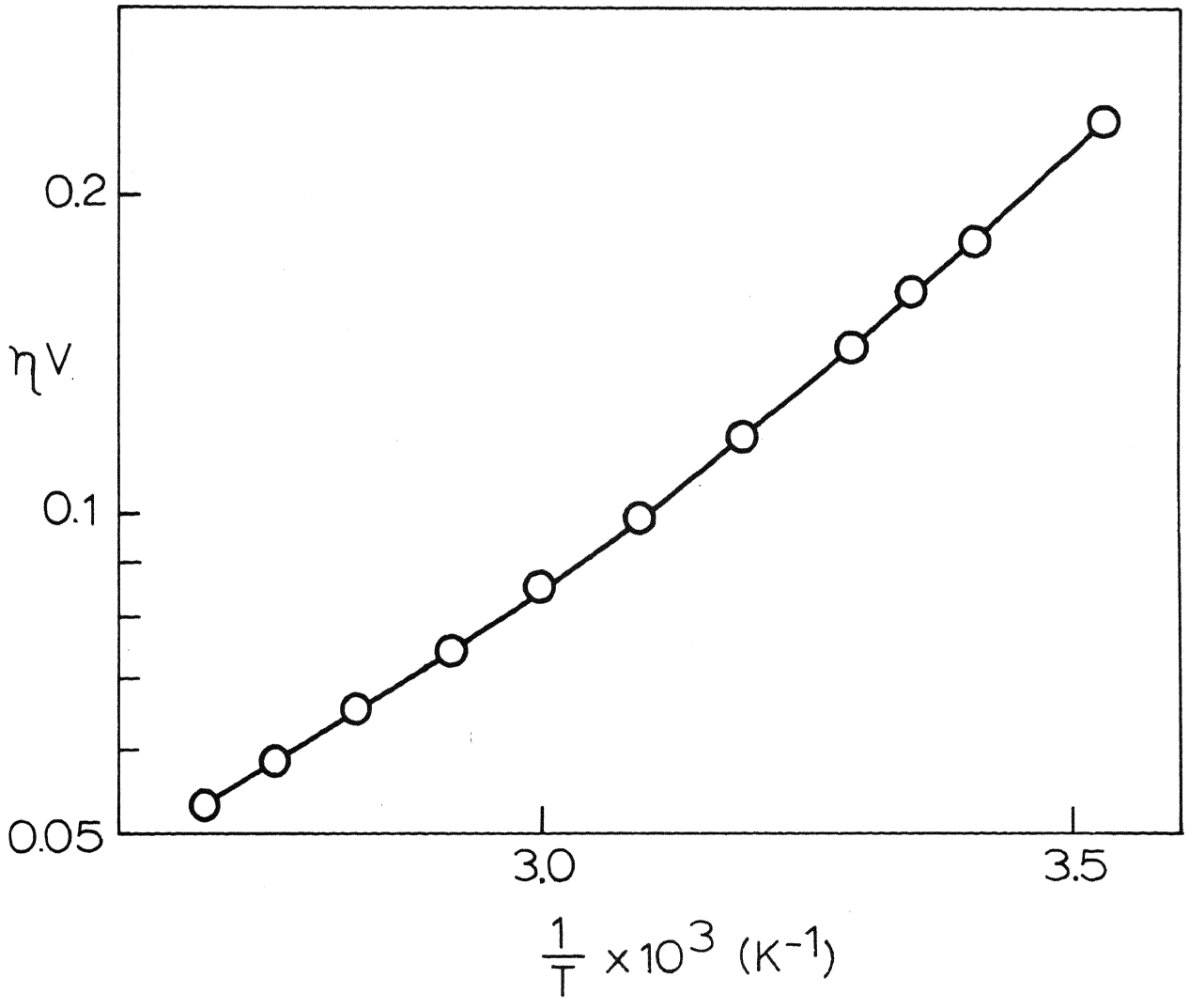

2.0
1.0
0.5
η(cp)
3.0
3.5
1/T x 10^3 (K^-1)

FIGURE II-3

EYRING PLOT OF WATER VISCOSITY


0.2
0.1
0.05
ηV
3.0
3.5
1/T x10^3 (K^-1)

- 105 ± 4 J/K-mol results. The value is somewhat large, since the heat capacity of bulk water molecules is only 76 J/K-mol. The magnitude of $\Delta C_p^{\neq}$ should not be taken seriously, since part of the temperature dependence of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ is usually not greater than the error of measurement.[24-26] With the aid of equations 6 and 12 the value of $\Delta S^{\neq}$ can be calculated. Table II-2 and Figure II-4 give the activation parameters at selected temperature values:

TABLE II-2. Thermodynamic Activation Parameters for the Viscous Flow of Water at Different Temperatures.

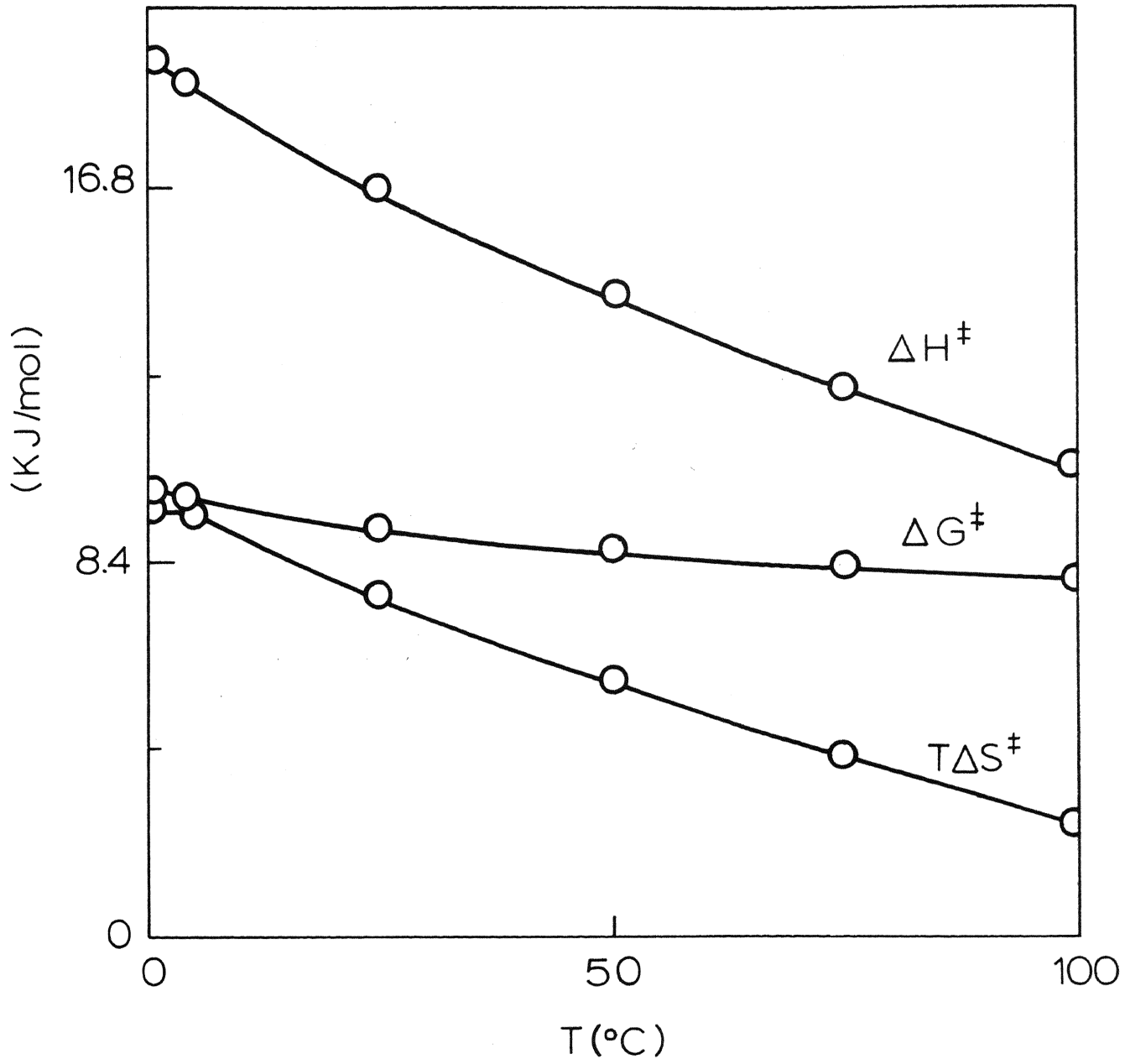
T (K)	$\Delta G^{\neq}$ (KJ/mol)	$\Delta H^{\neq}$ (KJ/mol)	$\Delta S^{\neq}$ (J/K-mol)
273.16	9.93	19.61	35.36
298.16	9.13	16.76	25.64
323.16	8.63	14.33	17.64
348.16	8.23	12.23	11.44
373.16	8.00	10.48	6.62

As is shown in Figure II-4, the upwards curvature of the $\Delta G^{\neq}$ curve indicates the predominant contribution of the enthalpy term to the free energy of activation. This result will be discussed later (*vide infra*).

The last result that we want to include in this account is the application of the *Proton Inventory* method to the study of the mechanism of momentum transport at the molecular level in liquid water. Since η measures the resistence to flow, the fluidity ($\Phi = 1/\eta$) must be the correct rate measurement to work with. Baker and La Mer[27] and Jones and Fernwalt[28] measured the relative viscosity of mixtures of light and heavy waters.

FIGURE II-4

THERMODYNAMIC ACTIVATION PARAMETERS FOR
THE VISCOUS FLOW OF WATER AT DIFFERENT TEMPERATURES


16.8
8.4
0
(KJ/mol)
ΔH‡
ΔG‡
TΔS‡
0
50
100
T(°C)

We shall use their results in this work. Figure II-5 shows the relative viscosity of such mixtures as a function of the deuterium atom fraction (n) and Figure II-6 their fluidity.

TABLE II-3. Relative Fluidity of Mixtures of Protium and Deuterium Oxides at 298.16 K.[27,28]

n	Φ_n/Φ_o
0.000	1.0000
0.006	0.9990
0.205	0.9569
0.222	0.9532
0.368	0.9242
0.428	0.9115
0.539	0.8912
0.550	0.8904
0.703	0.8613
0.709	0.8613
0.827	0.8410
0.848	0.8410
0.973	0.8169
0.980	0.8143

FIGURE II-5

VISCOSITY OF MIXTURES OF PROTIUM AND DEUTERIUM OXIDES

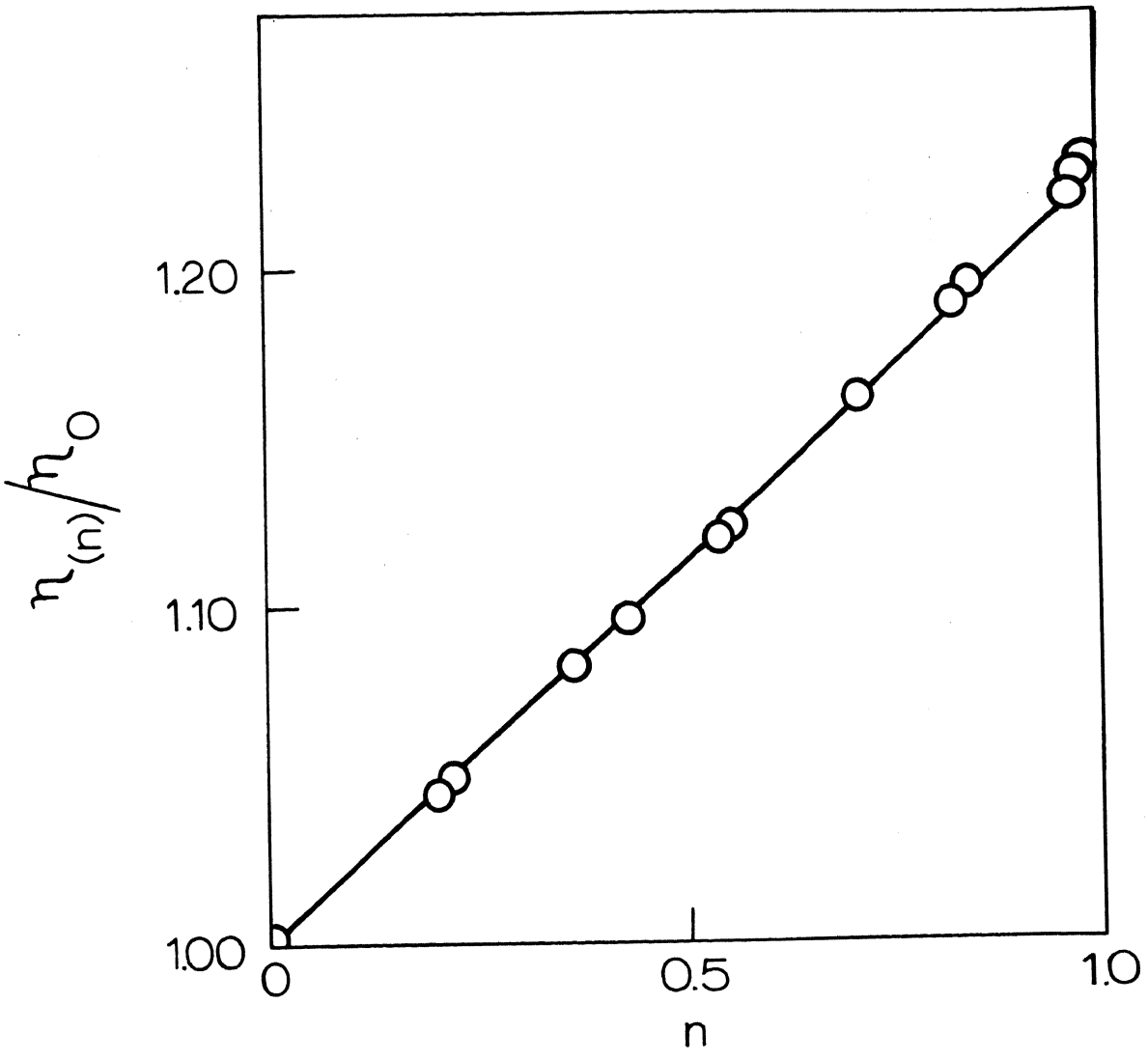
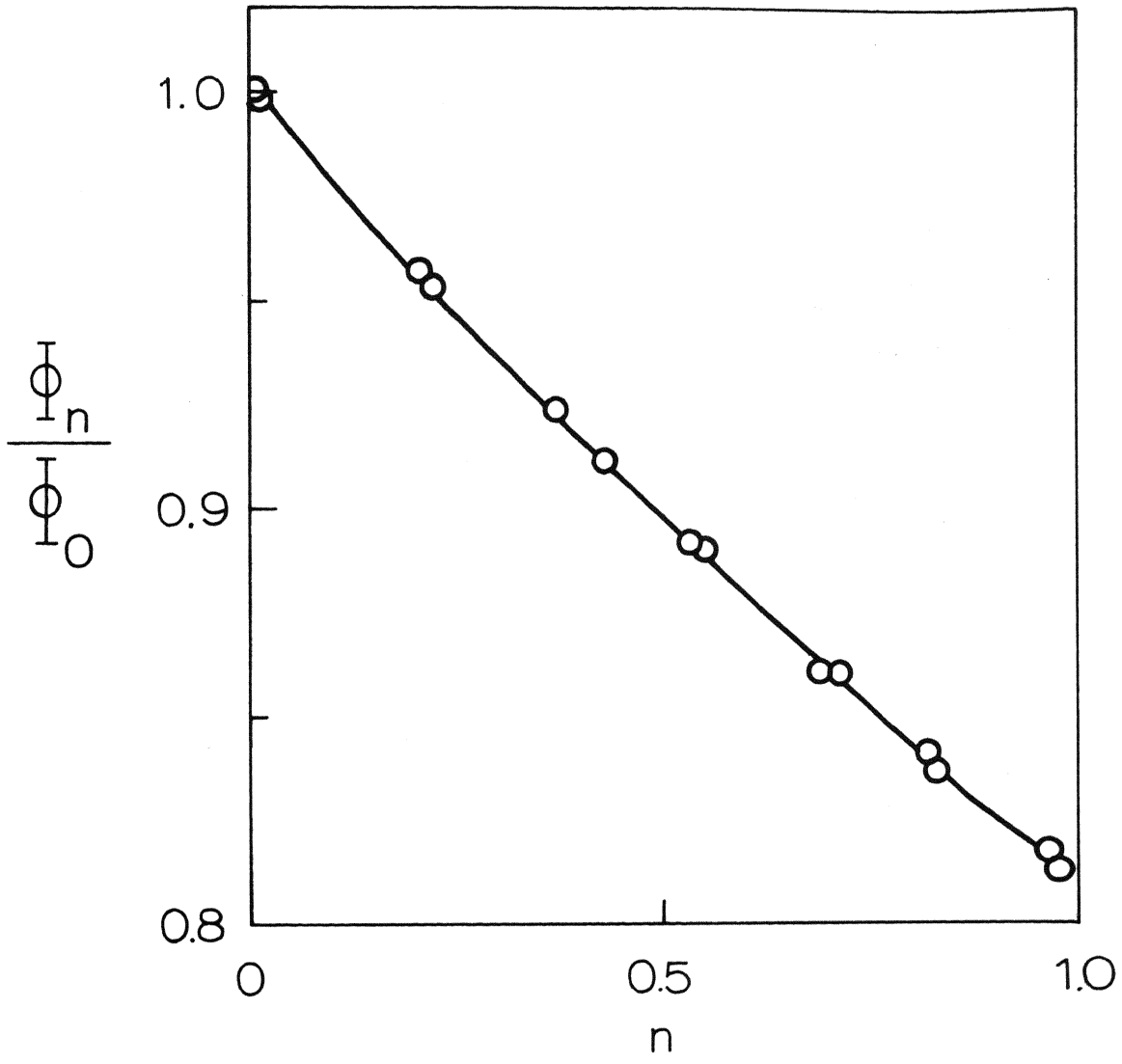

$\eta_{(n)}/\eta_0$
1.20
1.10
1.00
0
0.5
1.0
n

FIGURE II-6

PROTON INVENTORY FOR THE VISCOUS FLOW OF WATER AT 298.16 K


1.0
0.9
0.8
$\frac{\Phi_n}{\Phi_0}$
0
0.5
1.0
n

Since there is no contribution from the reactant state to the overall isotope effect (ϕ = 1 for bulk water), the fluidity - n data were directly submitted to polynomial fitting[22] and the following result obtained:

TABLE II-4. Analysis of Variance for the Proton Inventory Data for Viscous Flow of Water at 298.16 K.[23]

	F-value	F calc (%)
Linear Term	6814	17.8 (99.9)
Quadratic Term	329	16.8 (99.9)
Cubic Term	0.7	1.9 (80.0)

The above result suggests that a quadratic fit is significant to the 99.9% confidence level. This result can be expressed by equation 13:

$$\Phi_n/\Phi_o = (1 - n + n\phi)^2 \qquad (13a)$$

where Φ_n and Φ_o are the fluidities of a particular isotopic mixture and pure protium oxide, respectively, and from the fitting $\phi = 0.90 \pm 0.05$. With these results, an attempt will be made to propose a mechanism for the transport of momentum in liquid water.

Equation 13 can be expanded to give:

$$\Phi_n/\Phi_o = 1 - 0.20n + 0.01n^2 \qquad (13b)$$

and compared to the fitted polynomion:

$$\Phi_n/\Phi = 1 - (0.217 \pm 0.002)n + (0.029 \pm 0.002)n^2 \qquad (14)$$

DISCUSSION

General Comments. As was said in the Results Section, the negative volume of activation at room temperature indicates a transition state more closely packed but less structured than the molecules in the bulk of the system. The sign of the heat capacity of activation also suggests that the transition state of viscous flow is less structured than bulk "non-flowing" molecules. Both results agree with each other but do not give more detailed information on the structure of the transition state.

It was also mentioned in the Results Section that $\Delta H^{\neq}$ falls more repidly as temperature increases than $T\Delta S^{\neq}$ does. This result can be explained numerically with the following equation:

$$\frac{\partial(T\Delta S^{\neq})/\partial T}{\partial(\Delta H^{\neq})/\partial T} = 1 + \Delta S^{\neq}/\Delta C_p^{\neq} \qquad (15)$$

Since $\Delta C_p^{\neq}$ is a negative number whose absolute value decreases with rising temperature (see equation 12), and $\Delta S^{\neq}$ is a positive number, the rate of change of $T\Delta S^{\neq}$ is expected to be smaller than that of $\Delta H^{\neq}$. What is important is the physical meaning of this result. One can see that the structure of water breaks down smoothly when the temperature is elevated, but disorder is not introduced as quickly as bond breaking. Perhaps hydrogen bonds are not entirely broken but mostly weakened, thus introducing not very much molecular freedom in the system. This idea agrees with the finding that as temperature is raised, the coördination number of water remains practically constant but the mean distance between the molecules increases.[3b] According to the results of Bonner and Woolsey[15]

water should have only about 14% molar of the monomeric species at the boiling point, which is not really much. The existence of a correlation is immediately obvious: an isergonic-type relationship between the values of $\Delta H^{\neq}$ and those of $\Delta S^{\neq}$ at different temperature. The validity of this kind of relationship has been severely criticized,[24-26] but in the case at hand the physical reality of such a relation is obvious. Figure II-7 illustrates the result from which a direct correlation is seen between the breakdown of water structure and the concomitant acquisition of molecular freedom.

It seems that the temperature effect on the activation parameters is greater on the enthalpy and entropy of the ground state than on the transition state functions, since with values found in the literature[21] and those given in Table II-2 one can estimate that over the 100-degree range $H^{\neq}$ is about 18.5 KJ/mol and $S^{\neq}$ about 100 J/K-mol, while the corresponding values of the ground-state functions change appreciably.

Transfer of Momentum. With the ideas annoted in the previous section, it will be much easier to look into the mechanism of momentum transfer in water.

Suryanarayana[29] indicates that in all rate processes, the energy barrier to be overcome is the cohesive energy of the system in equilibrium. This postulate can be tested easily with the case at hand. A direct realtion should exist between the values of $\Delta H^{\neq}$ at different temperatures and the corresponding values of $p_i V$ where V is the molar volume of water.*

---

*The p_i values were calculated by means of the equation $p_i = T\alpha/\beta - p$ with values found in the literature,[21] and p = 1 atm.

FIGURE II-7

"ISOKINETIC" PLOT FOR THE VISCOUS FLOW OF WATER

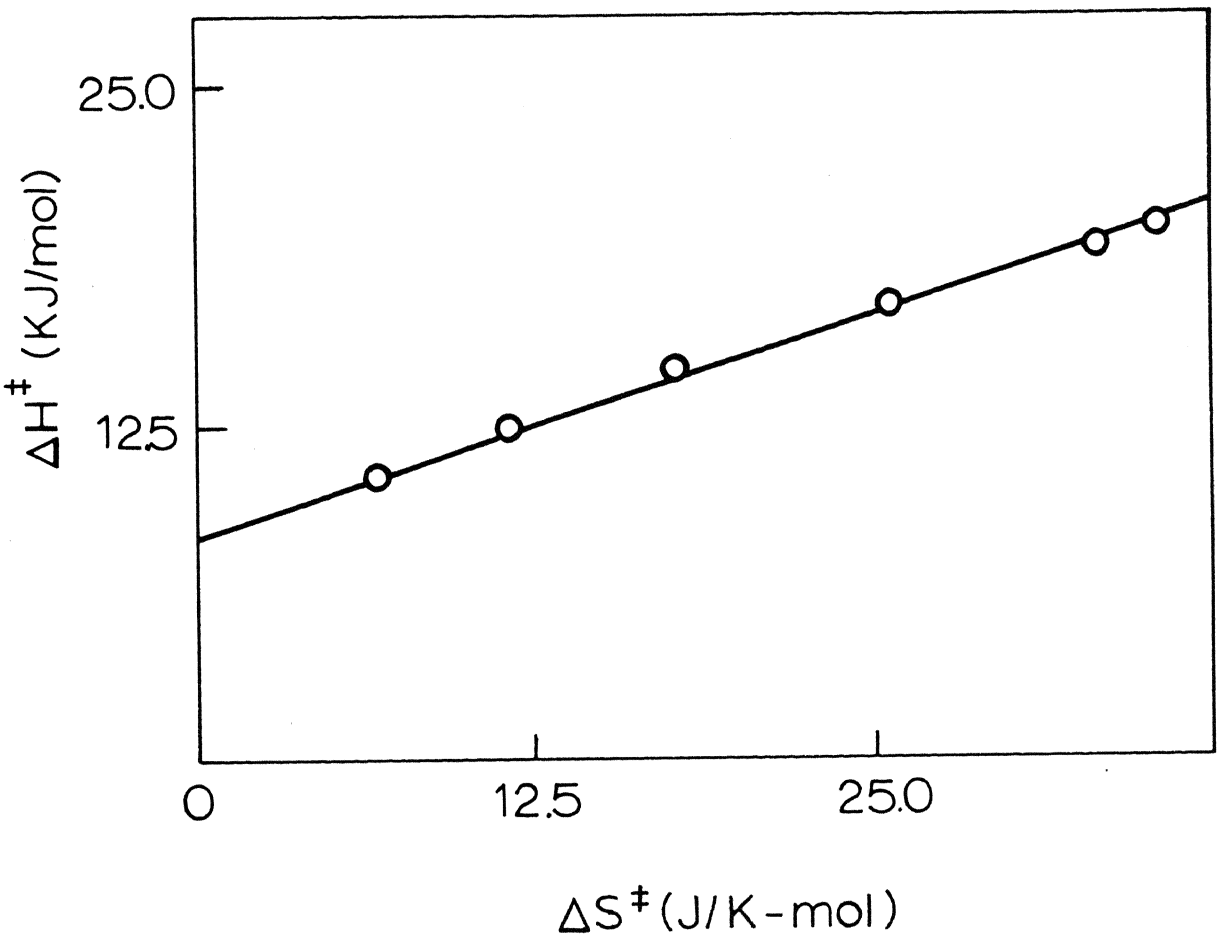

25.0
12.5
$\Delta H^{\ddagger}$ (KJ/mol)
0
12.5
25.0
$\Delta S^{\ddagger}$ (J/K-mol)

Figure II-8 shows such a correlation from 273 to 373 K in intervals of 12.5 K. At this point, the nature of the mechanism of viscous flow has gotten much clearer. Since a large part of the cohesive energy of water resides in the hydrogen bonds, and p_i can be correlated with $\Delta H^{\neq}$, the internal friction of water molecules is strongly suggested to work mainly *via* hydrogen bonds, that is, momentum is likely to be transferred by breaking hydrogen bonds between "flowing" layers.

The kinetic deuterium isotope effect on the viscous flow process of water shows a value of $\Phi_H/\Phi_D = 1.23$ at 298.16 K. Since the diffusing species in H_2O and D_2O are the same size (*vide supra*), one can safely say that there is no change in mechanism in going from light to heavy water.

The result from the *proton inventory* shows that two protons contribute to the observed isotope effect. The mechanism proposed below is based upon the conclusions obtained above. It explains well the obserbations reported in the Results Section.

Suppose two clusters exist with monomeric or interstitial water molecules between them. Assume also the existence of an equilibrium among the two clusters and the interstitial molecules. One cluster remains fixed while the molecules of the other begin to "jump" into neighboring holes under the action of an applied force. There is a transfer of momentum from the "flowing" cluster to the stationary one *via* the bridging molecules. Figure II-9 sketches the idea.

A small perturbation on the bonding potential of the "bridging" hydrogens is expected,as is indeed the case (10% isotope effect per deuterium).

FIGURE II-8

RELATION BETWEEN THE WATER ENTHALPY OF ACTIVATION OF VISCOUS FLOW AND THE INTERNAL PRESSURE OF WATER

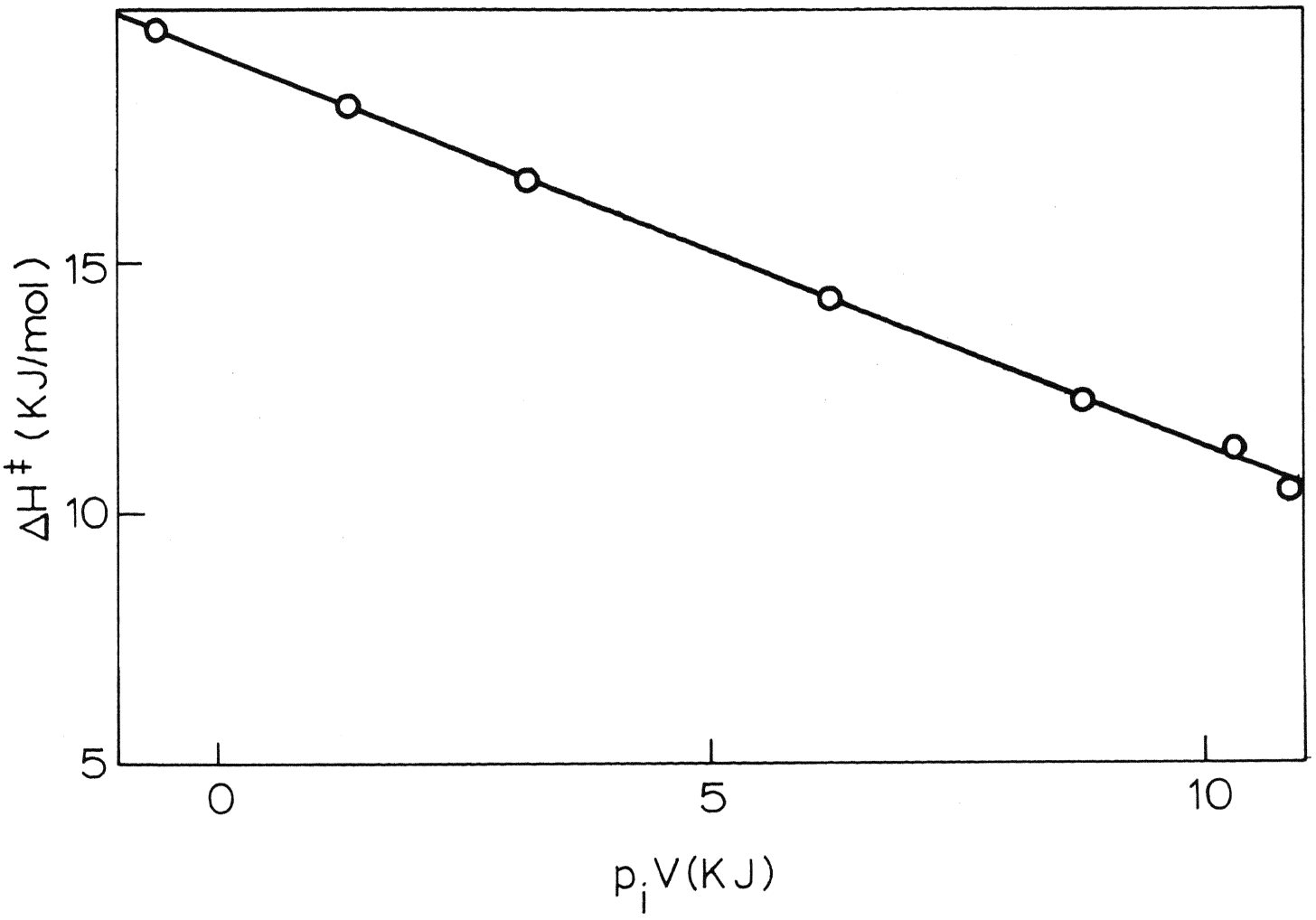
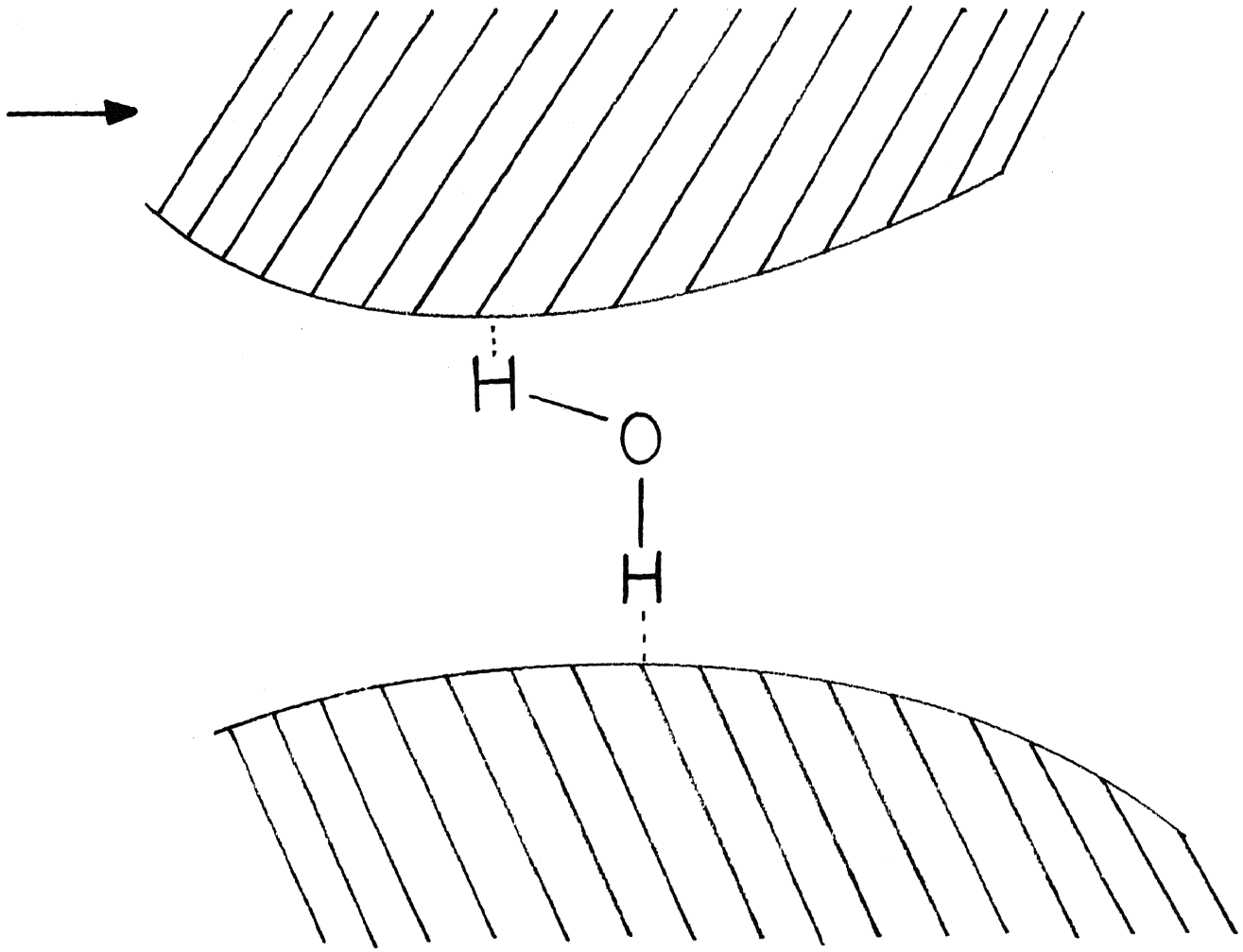

ΔH‡ (KJ/mol)
15
10
5
0
5
10
piV(KJ)

FIGURE II-9

PROPOSED MECHANISM FOR VISCOUS FLOW IN WATER


H
O
H

As one layer (cluster) goes past the other one, the "bridging" molecule will undergo a partial rotation. It is interesting to compare this idea with a previous suggestion[30,31] that in the case of water rotational motion is important for momentum transfer.

In the case of small alcohols, the viscosity can be expected to be lower than that of water, since the latter can form two hydrogen bonds per molecule. Since in water both hydrogens were found to contribute equally to the overall isotope effect, the easiest approach to the study of isotope effects on the viscosity of alcohols is to expect an isotope effect of 1.11. The observed values[32] are smaller than 1.11 and vary with the length and degree of remification of the chain, indicating a more complex situation than in water, since van der Waals forces play a much more important role in alcohols than in water.

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CHAPTER III

NEUTRAL HYDROLYSIS OF ESTERS

Structure and Reactivity of Carboxylic Esters. The molecular structure of carboxylic esters was recently reviewed by Jones and Owen,[1] therefore no attempt will be made to present that information here.

Carboxylic esters undergo nucleophilic addition, hydrolysis being a particular case. Hydrolysis can be brought about by acidic, basic, and nucleophilic catalysis. The special case where hydroxide ion acts as the nucleophile is called saponification. A recent communication[2] describes ester hydrolysis produced under the action of ultrasound. In principle, even the application of magnetic fields to an aqueous ester solution could produce the hydrolytic process since pH changes have been reported[3] (though also denied[4]) in water by the application of magnetic fields.

Esters which contain electron withdrawing groups in the acyl protion have been observed to undergo "neutral hydrolysis,"[5] that is, in the presence of neither acids or bases. The ease of product formation can be explained in terms of the fact that the electronegativity of the group attached to the carbonyl enhances its electrophilic character and thus promotes addition to the carbonyl double bond. As is expected, the greater the electronegativity of the substituent the faster the reaction rate. In Figure III-1 a correlation is shown for some substituted ethyl acetates in which the $\delta_x pK_a$ of the respective acids has been taken as a measure of the electronegativity of the substituted residue relative to the methyl group. Stable addition compounds of some alkyl[6-7] and aryl[8] trifluoroacetates with ethoxide ion have been studied by infrared spectroscopy in inert solvents and

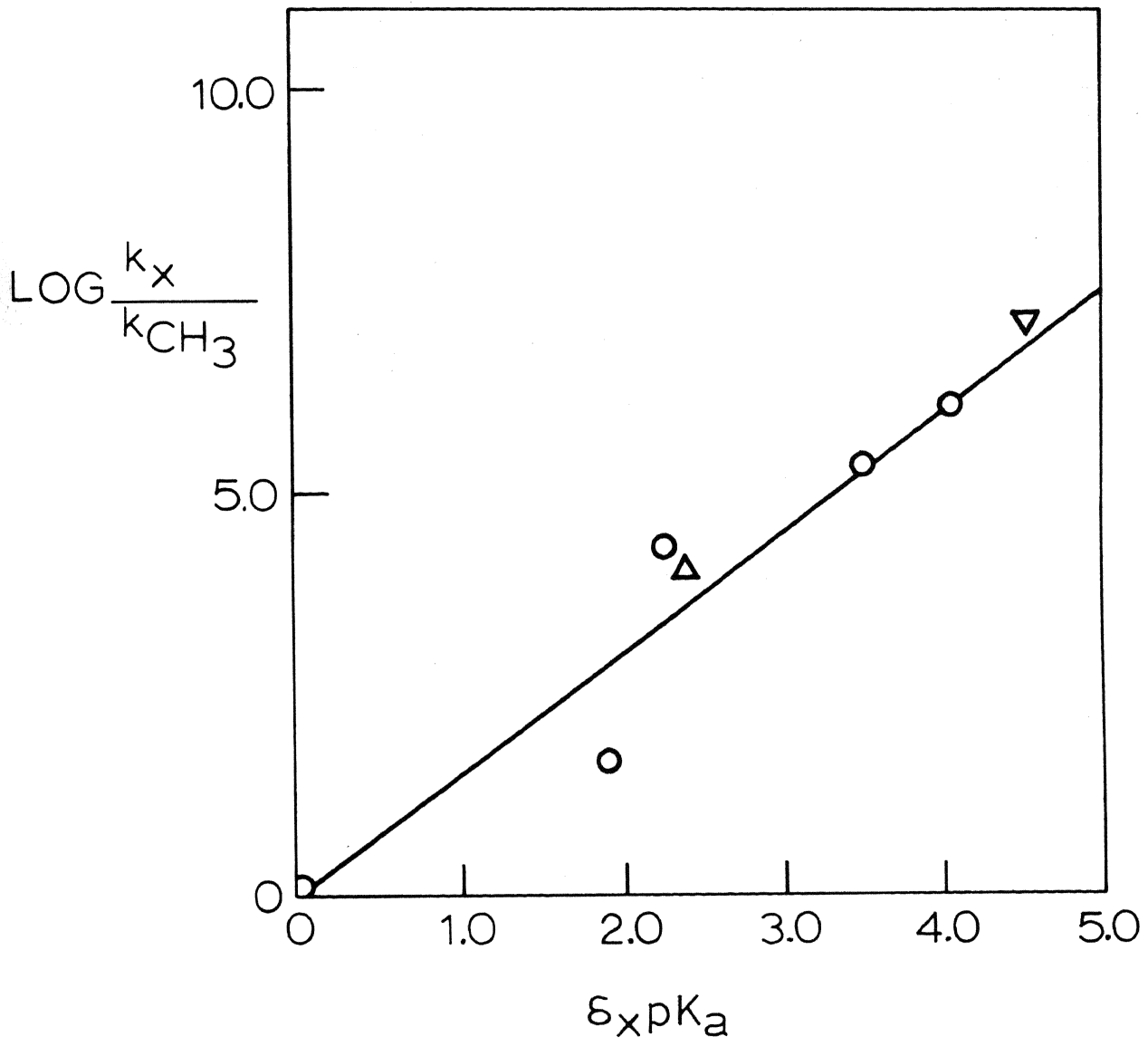
FIGURE III-1

RATES OF NEUTRAL HYDROLYSIS OF SOME SUBSTITUTED ETHYL ACETATES, 298.16° K

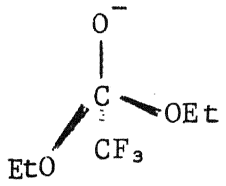
○ Reference 22

△ Reference 26

▽ This Work


10.0
5.0
0
LOG $\frac{k_X}{k_{CH_3}}$
0
1.0
2.0
3.0
4.0
5.0
$\delta_X pK_a$

shown to have the following structure.



The stability of these compounds is a function of the solvent and the nature of the cation. An electrostatic approach to the effect of electron withdrawing groups in the saponification of substituted acetates has been given by Barthel, Bäder, and Schmeer[9] but it will not be discussed here.

The Neutral ("Water") Hydrolysis of Carboxylic Esters. This kind of "spontaneous" reactions is found whenever there is a pH-independent flat valley in the rate-pH profile. Many sources of information relevant to the neutral hydrolysis of esters have appeared in the literature,[10-13] and also there is a whole volume in "Comprehensive Chemical Kinetics"[14] devoted to ester hydrolysis in general. A brief historical account of this problem will be given along with some general considerations. It is observed that if a reaction is catalyzed by either acids or bases, like the case of ester hydrolysis, the phenomenological rate constant gives a satisfactory fit to the equation[27]

$$k_{obs} = k_o + k_H[H^+] + k_{OH}[OH^-] + \sum_a [HA] + \sum_b k_b[B] \qquad (1)$$

where k_o is the "water" catalyzed reaction rate, and the other terms have their usual significance. Since in many cases[15] k_o falls on the same Brønsted plot as the rate constants for other general base catalysts, general base catalysis from water (on water) is suggested. The main

features of "water" reactions are[15,16] large kinetic solvent isotope effects (KSIE) in the range 2.0 - 4.0. The value of entropies and volumes of activation are large and negative ($\Delta S^{\neq}$ -84 to -210 J/deg-mole; $\Delta V^{\neq}$ -19 x 10^{-6} to -22 x 10^{-6} m^3/mole). These features point to some kind of special solvent arrangement which could be due to a transition state in which a large number of solvent molecules are "frozen" and under the effect of electrorestrictive forces associated with the stabilization of developing charges and the transfer of protons. The rates of these reactions are greatly retarded by concentrated solutions of certain salts. This inhibition has been attributed to a decrease in the activity of water and/or to a possible "manifestation of the interaction of salts with polar carbonyl compounds..."[15] This last statement deserves considerable thought. The stretching force constant of the C=O bond of acetone has been reported to be decreased by silver ion as well as the integrated density of such mode in the presence of alkali and alkaline-earth ions.[17]

A quasi-thermodynamic approach to general acid-base catalysis of reactions in water has been given by Jencks[18] in the form of a rule which is essentially a more "plastic" version of the principle of minimum action.[19] The rule says[18]: "concerted general acid-base catalysis of complex reactions in aqueous solutions can occur only (a) at sites that undergo a large change in pK in the course of the reaction, and (b) when this change in pK converts an unfavorable to a favorable proton transfer with respect to the catalyst; *i.e.*, the pK of the catalyst is intermediate between the initial and final pK values of the substrate site." This rule simply says that the

spontaneity of the process should be assured by an overall favorable change in the Gibbs function, since intuitively it is easy to see that for a concerted process there will be unfavorable comtributions to the enthalpy and entropy changes.

On the basis of ^{18}O tracer experiments, Bunton and Hadwick[20] have concluded that the spontaneous hydrolysis of methyl trifluoroacetate takes place by an acyl-oxygen fission mechanism. In contrast to this fact, Moffat and Hunt[21] consider that t-butyl trifluoroacetate reacts in acetone-water mixtures by a carbonium ion (S_N1) mechanism due to the fact that the extent of olefin formation in this reaction is similar to that produced by the t-butyl halides reacting in the same medium. Winter and Scott[22] studied the neutral hydrolysis of some alkyl trifluoroacetates at different temperatures in protium and deuterium oxides. From these studies, the authors were able to obtain the corresponding activation parameters ($\Delta H^{\neq}$, $\Delta S^{\neq}$). Their conclusions were essentially the same as those of Bunton and Hadwick and of Moffat and Hunt (*vide supra*). The following are results for the neutral hydrolysis of ethyl trifluoroacetate at 298.16° K taken from the paper of Scott and Winter.[22]

TABLE III-1. Activation Parameters for the Neutral Hydrolysis of Ethyl Trifluoroacetate at 298.16° K.[22]

$\Delta H^{\neq}$	40 KJ/mole
$\Delta S^{\neq}$	-159 J/K-mole
$\Delta Cp^{\neq}$	-281 J/K-mole

Later, Barnes, Cole, Lobo, Winter and Scott[23] applied the *proton inventory* method to the neutral hydrolysis of ethyl trifluoroacetate at 10° C, but the authors did not offer any definite explanation of their results.

A bibliographical list of publications concerning the neutral hydrolysis of esters is given in the appendix.

Statement of the Problem. The *proton inventory* method will be applied to the neutral hydrolysis of ethyl trifluoroacetate at 298.16° K. These results and those of Scott *et al.*[23] will be studied to find how many protons are responsible for the observed solvent isotope effect, and the contribution from each one.

Results. The following are the data reported by Scott *et al.*[23] for the neutral hydrolysis of ethyl trifluoroacetate at 283.16° K in mixtures of light and heavy water.

TABLE III-2. Observed First-Order Rate Constants for the Neutral Hydrolysis of Ethyl Trifluoroacetate at 283.16° K in Mixtures of Protium and Deuterium Oxides.[23]

n	$k_n \times 10^4$, sec^{-1}
0.000	12.476 ± 0.021
0.122	10.532 ± 0.030
0.225	9.505 ± 0.026
0.358	7.913 ± 0.018
0.434	7.498 ± 0.010
0.534	6.547 ± 0.013
0.751	5.101 ± 0.015
0.773	4.821 ± 0.012
0.892	4.061 ± 0.008
0.993	3.503 ± 0.006

Since there is no contribution from the reactant state to the KSIE, the data gives the transition state contribution directly. This set of data was submitted to polynomial regression fitting[24] and the result is given below.

TABLE III-3. Analysis of Variance for the Data of the Group of Scott.[24]

	F-Value	Calculated F (%)
Linear Term	368	25.4 (99.9)
Quadratic Term	49.6	29.2 (99.9)
Cubic Term	8.6	5.9 (95)
Quartic Term	1.8	2.2 (80)

Application of the F-test[25] indicates that the quadratic term is significant at the 99.9% confidence level and the cubic term at the 95% level. The data obtained in this laboratory at 298.16° K is shown in Table III-4.

TABLE III-4. Observed First-Order Rate Constants for the Neutral Hydrolysis of Ethyl Trifluoroacetate at 298.16° K in Mixtures of Protium and Deuterium Oxides.

n	$k_n \times 10^4$, sec^{-1}
0.000	34.96 ± 0.55
0.082	31.27 ± 1.05
0.219	28.53 ± 0.23
0.257	26.35 ± 0.80
0.476	19.83 ± 0.10
0.514	18.95 ± 0.07
0.543	19.63 ± 0.30
0.616	17.60 ± 0.50
0.670	16.37 ± 0.58
0.901	12.27 ± 0.75
0.993	9.69 ± 0.28

The same statistical treatment was performed on this set of data and the result is given below.

TABLE III-5. Analysis of Variance for the Data of This Work.[25]

	F-Value	Calculated F (%)
Linear Term	75	29.3 (99.9)
Quadratic Term	0.1	2.1 (80)
Cubic Term	0.7	2.2 (80)
Quartic Term	0.1	2.4 (80)

Our results are graphically indistinguishable from those of the group of Scott (see Figures 2 and 3), but no term beyond linear is shown as significant, even at the 80% confidence level, due to the poorer quality of our data. Thus, we conclude that for this reaction it is probable that three protons contribute to the observed solvent isotope effect, and a four-proton contribution is possible (*vide infra*).

FIGURE III-2

NEUTRAL HYDROLYSIS OF ETHYL TRIFLUOROACETATE IN MIXTURES OF LIGHT AND HEAVY WATER AT 298.16 K AND 0.1 *M* $LiClO_4$

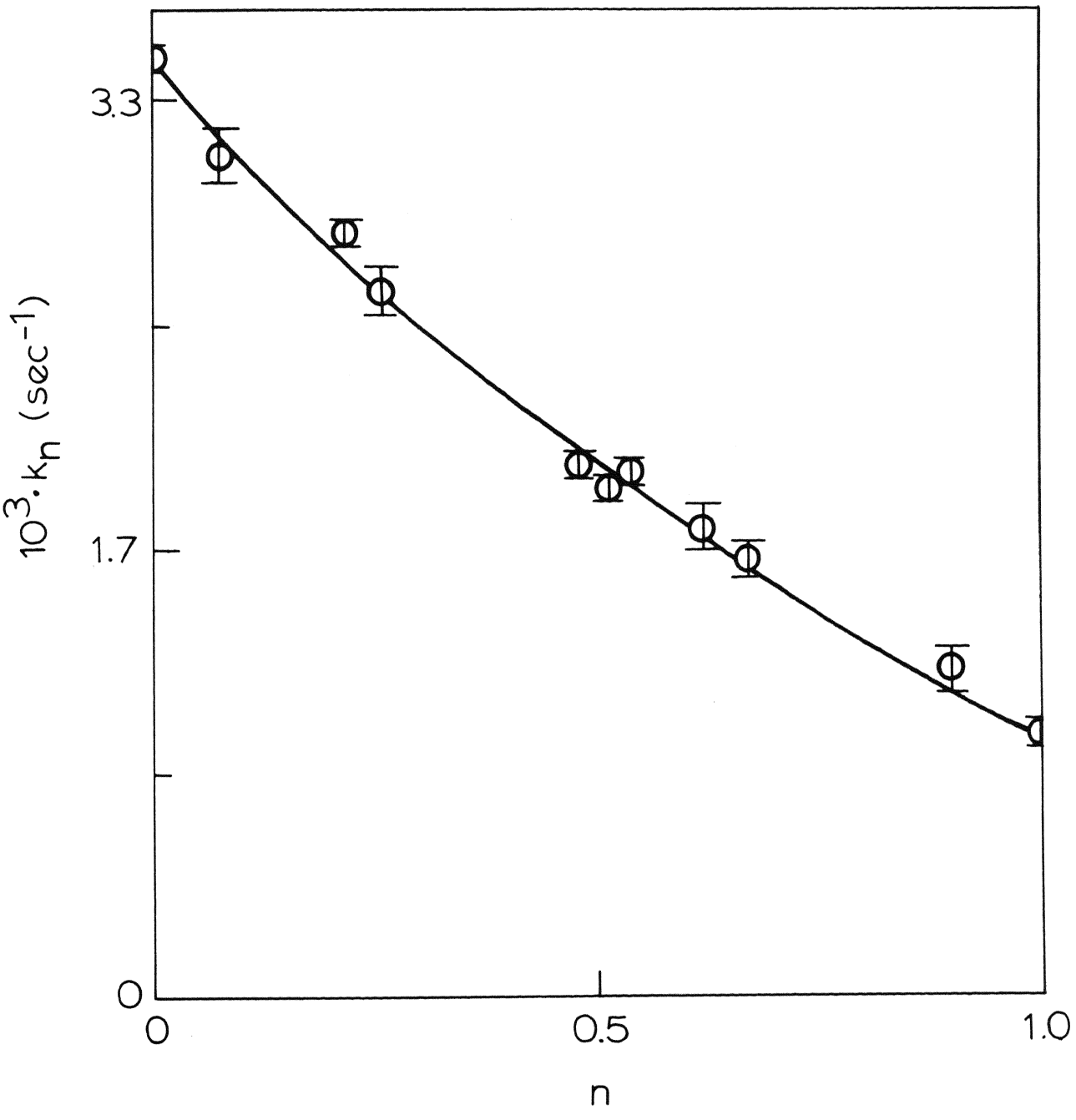
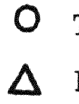
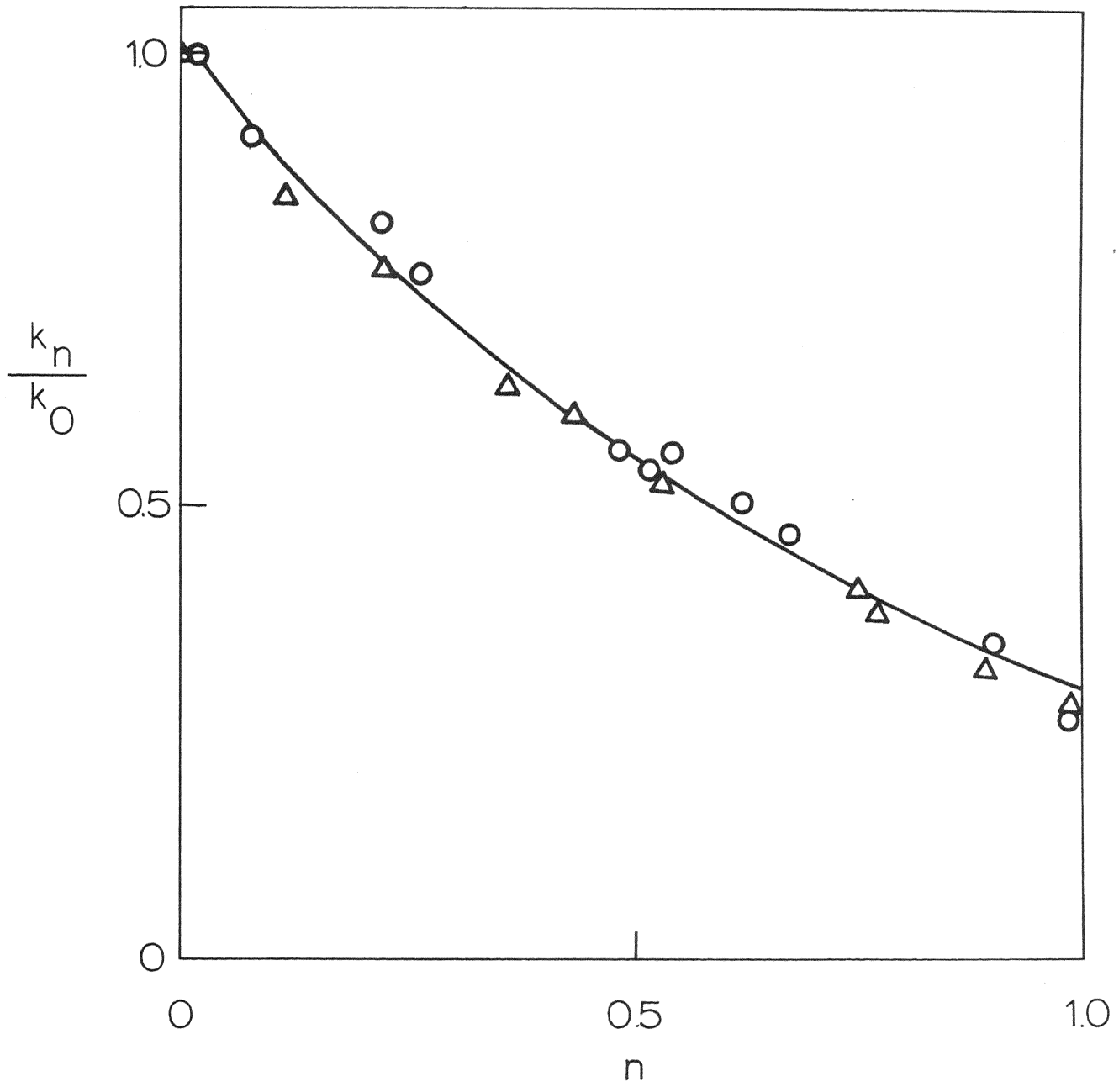

3.3
1.7
0
$10^3 \cdot k_n$ (sec^{-1})
0
0.5
1.0
n

FIGURE III-3

NEUTRAL HYDROLYSIS OF ETHYL TRIFLUOROACETATE IN MIXTURES OF LIGHT AND HEAVY WATER AT 283.16 AND 298.16 K




1.0
0.5
0
$\frac{k_n}{k_0}$
0
0.5
1.0
n

DISCUSSION

Bender and Heck[28] studied the hydrolysis of ethyl trifluoroacetate in mixed solvents. They arrived at four main conclusions:

a) There is an intermediate in the hydrolysis of esters.

b) The activation energies are identical for breakdown of the intermediate to reactants or to products.

c) There is no acid or base catalysis of the breakdown of the intermediate either to reactants or to products, that is, the partition of the intermediate is symmetrical.

d) The rate limiting step is attack of water at the carbonyl carbon of the ester.

Bender's proposition of slow addition of water to the carbonyl carbon of the ester was also suggested from our experiments on the infrared and ultraviolet spectroscopy of the system. In an earlier paper,[7] Bender showed that the carbonyl stretching band appears in the infrared spectra of ethyl trifluoroacetate dissolved in aqueous ethyl ether, methanol and ethanol, thus ruling out the possibility of instantaneous addition. In this work, the ultraviolet spectrum of methyl trifluoroacetate in methanol was obtained, the same as ethyl trifluoroacetate in ethanol. The spectra show the typical carbonyl band around 215 nm with $\varepsilon \sim 50$. The infrared spectrum of methyl trifluoroacetate in deuterium oxide taken right after dissolving the ester also shows the carbonyl stretching band at 1760 cm^{-1}.

This result agrees with the three-proton result of this work. The data can be expressed by an equation of the following general form:

$$k_n = k_o(1 - n + n\phi_1^*)(1 - n + n\phi_2^*)^2 \qquad (1)$$

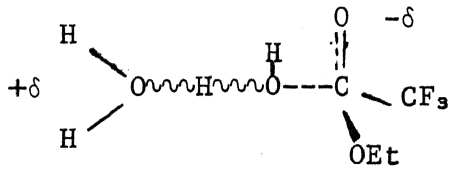
To support this assumption see Figure III-4 in which $f(n)$ expresses the following:

$$f(n) = \frac{k_n/k_o}{(1 - n + \phi_2^* n)^2} \qquad (2)$$

A plot of $f(n)$ *vs.* n should be linear for the correct choice of ϕ_2^*. Using this approach one obtains the following values for the parameters:

$\phi_1^* = 0.47$	$\phi_2^* = 0.77$	at 283.16 K
$\phi_1^* = 0.47$	$\phi_2^* = 0.78$	at 298.16 K

Since the values of ϕ_2^* are not much different at the two temperatures, the values at 298.16° K will be used in this discussion. These results can be translated into mechanistic language and the following representation of the rate-determining transition state obtained:



Another isotope effect arises from the central hydrogen being transferred, and its value is given by $1/\phi_1^* = 2.13$ which is in good agreement with the accepted value of 2.2 ± 0.5 for such bridging hydrogens.[29] So, the contribution of the primary isotope effect is 61% of the total KSIE. The secondary isotope effect is $(1/\phi_2^*)^2 = 1.64$ or 1.28 per hydrogen.

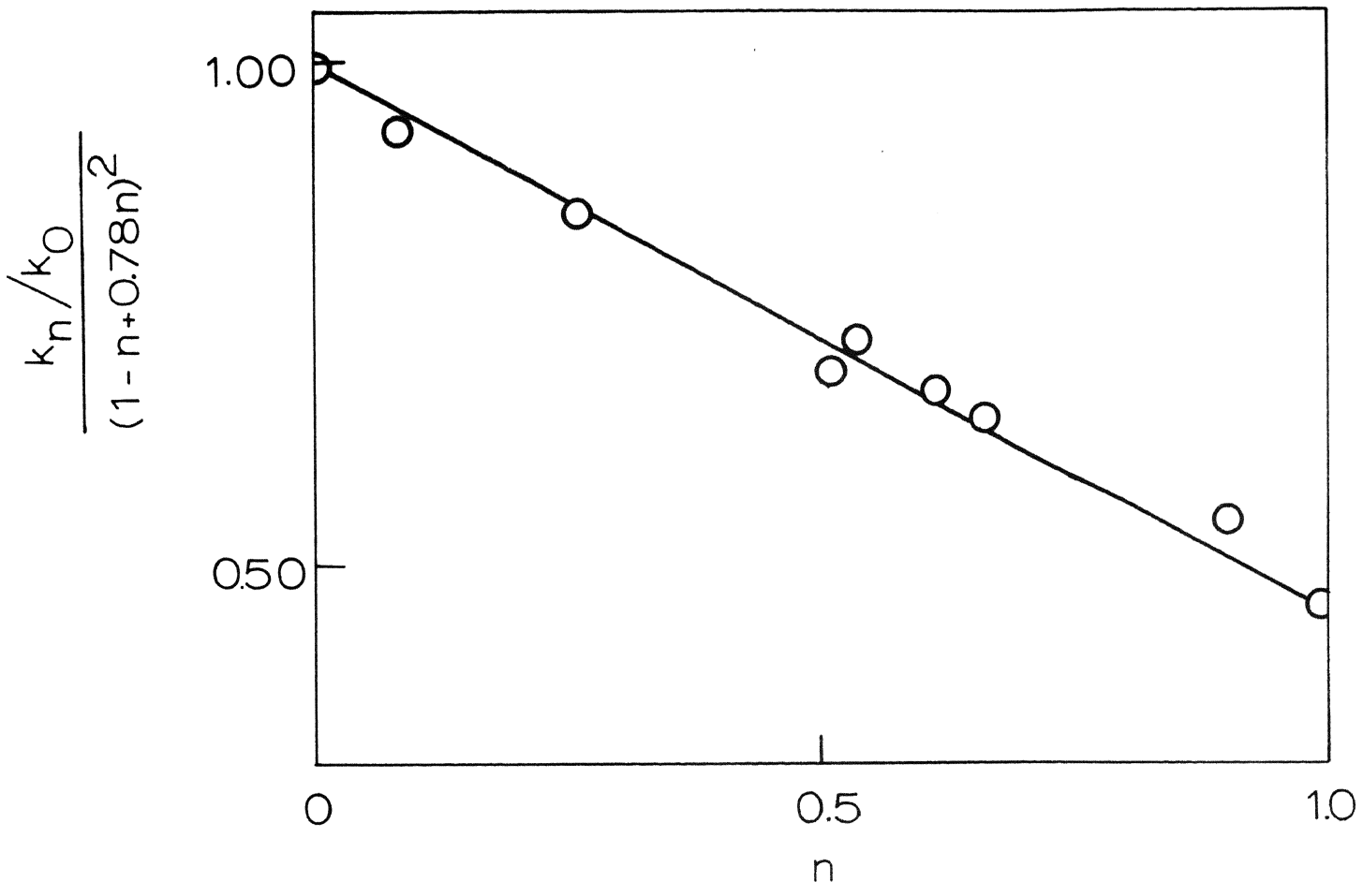
The value of δ in the transition state can be calculated as follows:[30]

$$\phi_2^* = \phi_R^{1-\delta}\phi_P^{\delta} \qquad (3)$$

where ϕ_R and ϕ_P are the isotopic fractionation factors of reactants and products, respectively. Since the reactants are water molecules and the

FIGURE III-4

GRAPHIC ANALYSIS FOR THE DATA ON NEUTRAL HYDROLYSIS OF ETHYL TRIFLUOROACETATE AT 298.16 K IN MIXTURES OF LIGHT AND HEAVY WATER


$\frac{k_n/k_0}{(1-n+0.78n)^2}$
1.00
0.50
0
0.5
1.0
n

ester, $\phi_R = 1.0$, and the products are hydronium ions, with $\phi_P = 0.69$,[30] δ turns out to be equal to $\delta = 0.67$. Since the catalytic entity is not a full hydronium ion (only 67% hydronium ion character), it could be called a *paene*-hydronium ion. Up to now, the proton on the *gem*-diol like oxygen atom has not been assumed to contribute to the overall isotope effect. This assumption is mainly for convenience but is reasonable. The hydroxyl group of "tetrahedral" transition states should have an isotopic fractionation factor similar to that of a *gem*-diol, which is around 1.23 (*vide infra*).

The postulation of this concerted mechanism implies a large ΔpK_a on the ester moiety. The pK_a of fluoral hydrate [$CF_3CH(OH)_2$] was determined as a model for the tetrahedral intermediate and the value obtained was 10.6. Protonation of the carbonyl oxygen in the ester is not a spontaneous process ($pK_a \sim -6$)[31] while the protonation of the anion of the tetrahedral intermediate is a very favorable process. So, this situation complies with the requisites given by the rule of Jencks[18] to observe general base catalysis.

A more quantitative picture of the proposed transition state is given in Figure III-5.

The same catalytic feature is likely to be operative in other similar reactions. Figure III-6 represents a rough correlation. The function $g(n)$ was plotted against n and the obtained result is given below:

$$g(n) = \frac{k_n/k_o}{(1 - n + \sqrt{0.69}\, n)^2} = (0.98 \pm 0.01) - (0.55 \pm 0.02)n \qquad (4a)$$

$$g(n) \simeq 1 - n + 0.45n \qquad (4b)$$

FIGURE III-5

QUANTITATIVE DESCRIPTION OF THE PROPOSED TRANSITION STATE FOR THE NEUTRAL HYDROLYSIS OF ETHYL TRIFLUOROACETATE

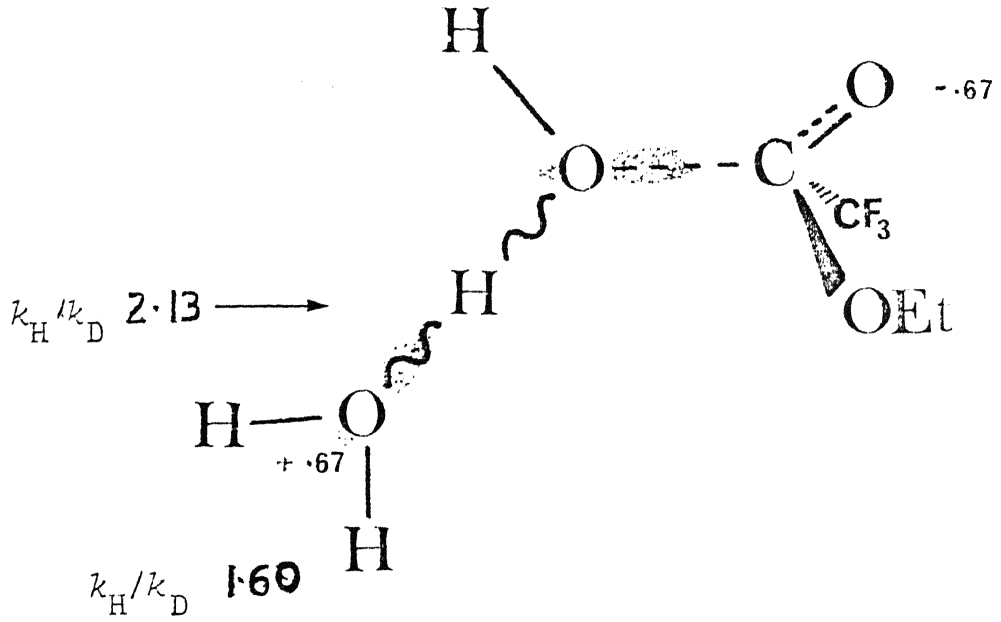

H
O
C
O
-·67
CF3
OEt
H
k_H/k_D 2·13
H
O
+·67
H
k_H/k_D 1·60

FIGURE III-6

Paene-HYDRONIUM ION AS A CATALYTIC ENTITY
IN THE NEUTRAL HYDROLYSIS OF CARBOXYLIC ESTERS

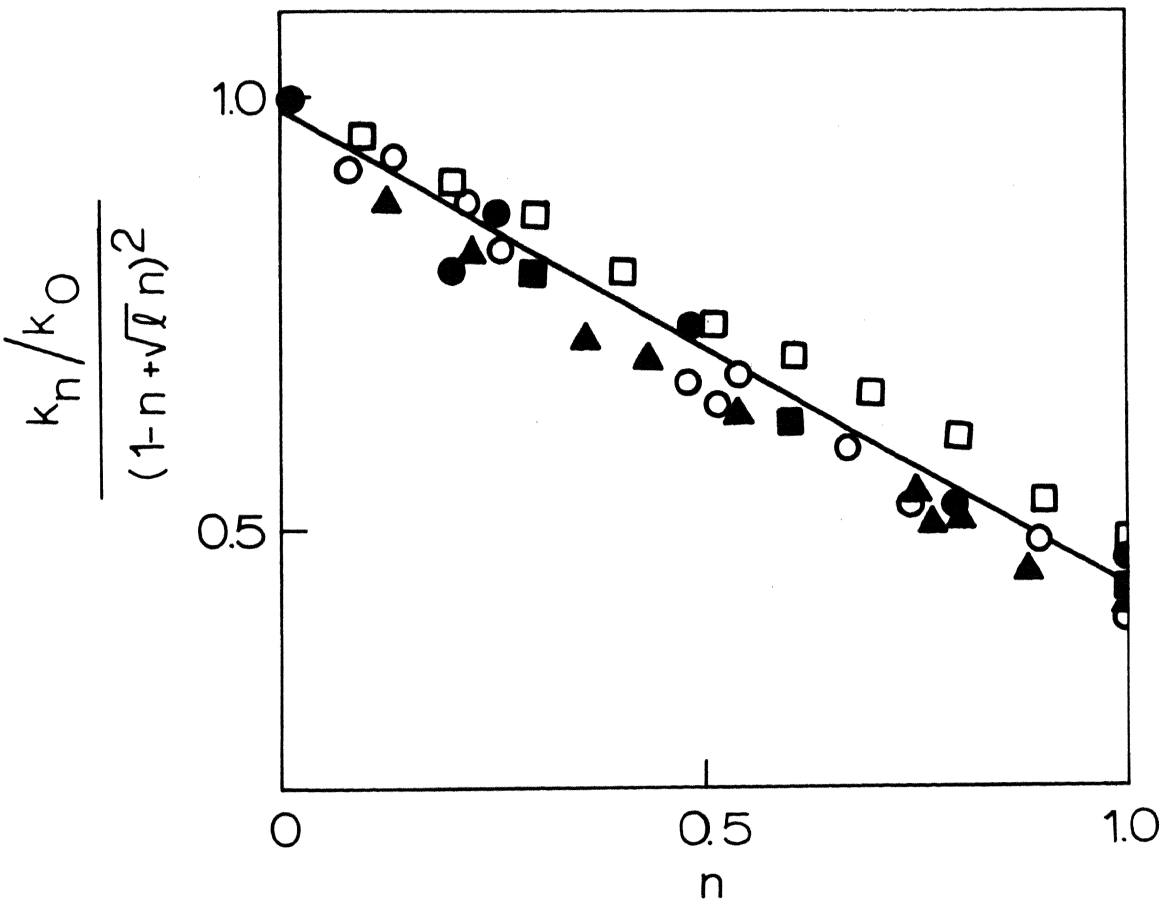
○ CF_3COOEt, 298.16 K, this work

▲ CF_3COOEt, 298.16 K, reference 23

● Et-*o*-$NO_2C_6H_4$ oxalate, 298.16 K, reference 34

■ Cl-CH_2-$COOCH_2Cl$, 298.16 K, reference 35

□ Ac_2O, 298.16 K, reference 36


$\frac{k_n/k_0}{(1-n+\sqrt{\ell}\,n)^2}$
1.0
0.5
0
0.5
1.0
n

The choice of $\phi = \sqrt{0.69}$ only intends to set a reference point at the exact hemihydronium ion. Of course, since the amount of hydronium ion likeness is different for every case, appreciable scattering is observed. Nevertheless, the correlation is acceptable and the *paene*-hydronium ion seems to be a common catalytic entity in the neutral hydrolysis of carboxylic esters and of acetic anhydride.

EXPERIMENTAL

Materials. Lithium perchlorate, anhydrous (the G. Frederick Smith Chemical Co.), methyl trifluoroacetate (K & K Laboratories, Inc), ethyl trifluoroacetate (Aldrich), and chlorophenol red (Fisher) were used as obtained. Acetonitrile (Mathieson, Coleman and Bell, spectro-quality) was dried over molecular sieves before use. Deuterium oxide was from Stohler Isotope Chemicals and was distilled before use.

Solutions. All solutions had lithium perchlorate to maintain the ionic strength at 0.1 *M*. The solutions were prepared as follows: The weight of a dry 25-ml volumetric flask was measured. To it was added approximately 1 mg of chlorophenol red and the weight of the flask plus the dye measured. Then, about 0.27 g of lithium perchlorate was added, and the same operation was repeated. Then, the necessary amount of deuterium oxide was added by syringe. Protium oxide was finally added to make up a total volume of 25 ml and its weight was determined.

Kinetic Measurements and Data Treatment. (Notebook Reference: Book I, P. 10) Kinetics were done on a Cary 16 ultraviolet-visible spectrophotometer equipped with a constant temperature device to keep the cell temperature at 298.16° K. The release of hydrogen ions was followed by measuring the disappearance of the red form of chlorophenol red at 590 nm. The combination of hydrogen ions with the dye is much faster than the hydrolysis reaction.[32] The cells were filled with the desired solution (3 ml) and allowed to attain temperature equilibrium either in the cell compartment or in the temperature bath. Then, a suitable amount of ester-acetonitrile stock solution (∿ 0.06 g/ml) was

injected into the cuvette.

The first-order rate constants were determined by submitting the absorbance-time data to the non-linear least squares computer program of Maw-Song Wang. Since different rate constants were obtained when less than 95% of the reaction data were fed to the computer, all rate constants were obtained by feeding data which were not less than the above extent of the reaction.

Determination of the pK_a of Fluoral Hydrate. (Notebook reference: Book I, pp. 65-67) A common potentiometric titration[33] was done in the thermostated cell of a Radiometer pH-Stat at 298.16° K. The following procedure was followed: 25 µl of fluoral hydrate was dissolved in 25 ml of deionized distilled water in the pH-Stat cell. Then, small amounts of sodium hydroxide 0.1000 *M* were added from a 10 ml burette. The titration curve was fitted to a polynomial function.[24] The inflexion point was obtained by the usual procedure ($d^2pH/dc^2 = 0$) and the pK_a calculated.

Spectra. Ultraviolet spectra were taken with a Beckman DB-G grating spectrophotometer and infrared spectra on a Perkin-Elmer Infracord Spectrophotometer.

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APPENDIX

INDIVIDUAL RATE CONSTANTS

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RATE CONSTANTS FOR THE NEUTRAL HYDROLYSIS OF ETHYL TRIFLUOROACETATE
AT 25 DEGREES. IONIC STRENGTH= 0.1M (LITHIUM PERCHLORATE).

N=0.000


IRUN=   1
  ITERATION NUMBER=   3
    C1=    .14319E+00          SDC1=    .15890E-02
    C2=    .50676E+00          SDC2=    .13841E-02
    CK=    .21296E+00          SDCK=    .67243E-02

IRUN=   2
  ITERATION NUMBER=   3
    C1=    .14859E+00          SDC1=    .14184E-02
    C2=    .53534E+00          SDC2=    .13376E-02
    CK=    .19679E+00          SDCK=    .54586E-02

IRUN=   3
  ITERATION NUMBER=   2
    C1=    .15177E+00          SDC1=    .16094E-02
    C2=    .51077E+00          SDC2=    .14494E-02
C   CK=    .20628E+00          SDCK=    .62842E-02

IRUN=   4
  ITERATION NUMBER=   2
    C1=    .15754E+00          SDC1=    .14007E-02
    C2=    .45808E+00          SDC2=    .12371E-02
    CK=    .21022E+00          SDCK=    .53398E-02

IIII
```

```
  ITERATION NUMBER=   3
    C1=    .10204E+00          SDC1=    .14828E-02
    C2=    .32103E+00          SDC2=    .13583E-02
    CK=    .17264E+00          SDCK=    .65281E-02

IRUN=   3
  ITERATION NUMBER=   3
    C1=    .10195E+00          SDC1=    .12723E-02
    C2=    .26925E+00          SDC2=    .12451E-02
    CK=    .19037E+00          SDCK=    .63198E-02

IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII

N=0.257

IRUN=   1
        SLOPE=    -.1629E+00     STANDM=    .2663E-02
        B     =     .3500E+01     STANDB=    .2023E-01

IRUN=   2
        SLOPE=    -.1581E+00     STANDM=    .2213E-02
        B     =     .3090E+01     STANDB=    .1608E-01

IRUN=   3
        SLOPE=    -.1534E+00   STANDM  =    .3274E-02
        B     =     .3097E+01     STANDB=    .1937E-01

IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII

N=0.476

IRUN=   1
        SLOPE=    -.1186E+00     STANDM=    .8613E-03
        B     =     .3982E+01     STANDB=    .5035E-02

IRUN=   2
        SLOPE=    -.1362E+00   STANDM  =    .6937E-03
        B     =     .3990E+01     STANDB=    .4055E-02

IRUN=   3
        SLOPE=    -.1193E+00     STANDM=    .1081E-02
        B     =     .4006E+01     STANDB=    .6320E-02

IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII

N=0.515

IRUN=   1
        SLOPE=    -.1140E+00     STANDM=    .4644E-03
        B     =     .1304E+01     STANDB=    .4562E-02

IRUN=   2
        SLOPE=    -.1133E+00     STANDM=    .1007E-02
        B     =     .8402E+00     STANDB=    .1166E-01
```

```
N=0.543

IRUN=   1
  ITERATION NUMBER=   3
    C1=    .15491E+00          SDC1=    .46191E-02
    C2=    .51497E+00          SDC2=    .53051E-02
    CK=    .12623E+00          SDCK=    .96860E-02

IRUN=   2
  ITERATION NUMBER=   3
    C1=    .10991E+00          SDC1=    .17562E-02
    C2=    .41109E+00          SDC2=    .20126E-02
    CK=    .11579E+00          SDCK=    .44947E-02

IRUN=   3
  ITERATION NUMBER=   2
    C1=    .11481E+00          SDC1=    .14413E-02
    C2=    .45285E+00          SDC2=    .16537E-02
    CK=    .11822E+00          SDCK=    .36599E-02

IRUN=   4
  ITERATION NUMBER=   3
    C1=    .10438E+00          SDC1=    .13774E-02
    C2=    .44501E+00          SDC2=    .15817E-02
    CK=    .12718E+00          SDCK=    .43398E-02

IRUN=   5
  ITERATION NUMBER=   3
    C1=    .15076E+00          SDC1=    .93776E-03
    C2=    .40272E+00          SDC2=    .95774E-03
    CK=    .11934E+00          SDCK=    .22021E-02

IIII
```

```
  ITERATION NUMBER=   2
    C1=    .42470E+00          SDC1=    .36950E-02
    C2=    .10565E+00          SDC2=    .33592E-02
    CK=    .10068E+00          SDCK=    .23140E-02

IRUN=   2
  ITERATION NUMBER=   3
    C1=    .47049E+00          SDC1=    .38567E-02
    C2=    .26219E-01          SDC2=    .37997E-02
    CK=    .95695E-01          SDCK=    .20617E-02

IRUN=   3
  ITERATION NUMBER=   3
    C1=    .46912E+00          SDC1=    .29686E-02
    C2=    .19332E+00          SDC2=    .27796E-02
    CK=    .88288E-01          SDCK=    .14444E-02

IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII

M=0.900

IRUN=   1
  ITERATION NUMBER=   3
    C1=    .48917E+00          SDC1=    .58926E-02
    C2=    .66008E+00          SDC2=    .47624E-02
    CK=    .74024E-01          SDCK=    .19741E-02

IRUN=   2
  ITERATION NUMBER=   2
    C1=    .37911E+00          SDC1=    .36147E-02
    C2=    .96336E-01          SDC2=    .25005E-02
    CK=    .78653E-01          SDCK=    .16002E-02

IRUN=   3
  ITERATION NUMBER=   3
    C1=    .65726E+00          SDC1=    .10046E-01
    C2=    .12517E+00          SDC2=    .76014E-02
    CK=    .70057E-01          SDCK=    .22489E-02

IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII

N=0.993

IRUN=   1
  IEERATION NUMBER=   3
    C1=    .20696E+00          SDC1=    .27653E-02
    C2=    .76337E+00          SDC2=    .31466E-02
    CK=    .58112E-01          SDCK=    .16900E-02
```

APPENDIX II

SUPPLEMENTARY PARTIAL BIBLIOGRAPHY ON THE NEUTRAL HYDROLYSIS OF ESTERS

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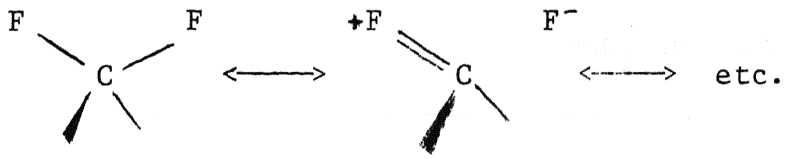
CHAPTER IV

FRACTIONATION FACTORS OF *Gem*-DIOLS AND RELATED COMPOUNDS

The Structure of Geminally-Substituted Compounds. The bond lengths between the central carbon atom and geminal electronegative substitutents are generally shorter than the corresponding bond lengths in mono-substituted molecules. For example, the C-F distance varies inversely with the number of fluorines on the same carbon.[1] This finding was explained in terms of double bond-no bond resonance:[2,3]



The same idea has been expressed in molecular orbital language.[4] Another explanation has been put forward by Peters[5] in which this author explains that the fluorine atom withdraws more *p* than *s* electron density from the carbon. Table IV-1 shows the carbon-fluorine bond distances for the fluorinated methanes:

TABLE IV-1. C-F Bond Distance in Simple Fluorinated Compounds.[1]

Compound	C-F, Å
CH_3F	1.39
CH_2F_2	1.36
CHF_3	1.33
CF_4	1.32

In the case of cyclic compounds, the presence of two oxygen atoms attached to the same carbon leads to considerably increased stability.[3] Table IV-2 shows the gas phase heat of formation of some cyclic compounds.

TABLE IV-2. Heats of Formation of Some Cyclic Ethers.

Compound	$-\Delta H_f$ (KJ/mol)
Cyclohexane	123.6
Tetrahydropyran	220.4
1,4-Dioxane	318.4
1,3-Dioxane	346.1
Cyclopentane	77.5
Tetrahydrofuran	182.3
1,3-Dioxolane	302.9

Direct structural determinations have been made on compounds such as chloral hydrate[6] and dimethoxymethane[7,8] and their molecular geometry found not to agree with that expected on the assumption of simple alcohols and ethers.

Gem-diols are the products of the general reaction:

$$R_2CO + H_2O = R_2C(OH)_2$$

Most of them exist only in solution, and are not stable enough to be isolated. Some aldehydes and ketones with electron withdrawing groups give the isolable product.

Theoretical studies have recently been undertaken in order to obtain

information related to the structure of *gem*-diols and hemiacetals.[9-11,20] Pople, *et al.*,[9] recently published an *ab initio* study on formaldehyde hydrate (methanediol) and found the internal rotation potentials to be strongly coupled and the bond lengths to be dependent on conformation. Depending on the particular conformation the molecule is in, the rotational barrier can vary from 26 to 46 KJ/mol. A semiempirical CNDO/2 study appeared later by Traux, *et al.*,[11] in which the authors dealt with perfluoroacetone hydrate (hexafluoropropane-2,2-diol). In this case, the problem is more complicated to interpret due to the possibility of internal hydrogen bonding (-O-H---F). They found the hydroxyl torsional barrier to be of the order 8 KJ/mol. Similar results were found in the study of Tvaroška and Bleha[20] on the rotational potential of dimethoxymethane (16 KJ/mol). From this brief account, one can see that in more contemporary language, the notion of double bond-no bond resonance in geminally-substituted molecules should be considered as some sort of back bonding between the "non-bonding" orbitals in the substituents and the central carbon. In other words, this double bond character that appears to be present in *gem*-compounds could be explained basically in the following form.[9,12,13] When electronegative atoms with "non-bonding" orbitals are attached to the same carbon atom, the substituents withdraw electron density from the central atom *via* σ bonds. Then, the bonding capacity of this particular carbon atom has not been satisfied and the neighboring "non-bonding" orbitals share their electron density with the partly vacant carbon orbitals. Further discussion of this non-classical type of interaction will be considered later in another section. Experimental evidence of this "saturated" delocalization in some molecular

species has been obtained recently from microwave spectral studies of *O*-methyl hydroxylamine[29] and methylhydrazine[28] as well as in calorimetric measurements on the addition of amines to formaldehyde.[30]

The Nature of Isotopic Fractionation Factors. Consider a solute with one hydrogenic position, SH, being dissolved in an isotopic solvent mixture of ROH and ROD:

$$SH + ROD = SD + ROH$$

$$\phi = \frac{[SD]/[SH]}{[ROD]/[ROH]} \qquad (1)$$

The equilibrium constant ϕ is called the *isotopic fractionation factor* of the hydrogenic position of SL. This quantity expresses the discrimination of protium for deuterium in the hydrogenic site of SL relative to the same preference in the solvent. For any particular site in a molecule the corresponding *isotopic fractionation factor* is defined analogously. In the case of water, which contains two exchangeable hydrogens, it is assumed that the preference for deuterium over protium of one of the hydrogenic sites is independent of whether there is a protium or a deuterium occupying the other position and that the preference for deuterium in both positions is the same in all possible isotopic configurations (rule of the geometric mean).[14] The same applies to any solute with more than one exchangeable position.

The following approach can be taken to fully appreciate the structural meaning of fractionation factors. When ϕ is set in terms of the isotopic ratios of the corresponding partition functions and the gas phase, rigid rotor, harmonic oscillator approximation taken, ϕ can be written as follows:

$$\phi = \text{MMI} \times \text{EXC} \times \text{ZPE} \qquad (2)$$

where the MMI term (mass, moment of inertia) contains the product of molecular weights and moments of inertia; the EXC or excitation factor accounts for the population statistics of the upper levels; and the ZPE or zero point energy term gives the difference in vibrational zero point energy between the reactants and products[15] (or transition states).

From equation 2 it is evident that fractionation factors contain geometrical information. The last two terms in equation 2 are functions of the molecular dynamics, that is, of the vibrational frequencies, ν_i, which in turn are simply related to the corresponding force constants. Thus, fractionation factors tell basically about the difference between the bonding potentials of hydrogens in the i-th site of the molecule of interest and in the solvent.

When the value of ϕ is greater than 1, it tells that deuterium accumulates in the i-th site of the molecule of interest preferentially to solvent molecules. This means that hydrogens are more tightly bound in SL than in the solvent molecules. Likewise, if the value of ϕ is smaller than 1 hydrogens are bound loosely in the i-th site of the substrate molecule relative to solvent molecules.

Determination of Isotopic Fractionation Factors by Means of Nuclear Magnetic Resonance Spectrometry. This method[16-18] is based on the fact that hydrogen exchange between water (or alcohols) and many solutes is very rapid compared to the N.M.R. time scale. Thus, *the only signal which is obtained is the weighted average of the positions of every exchangeable proton:*[19]

$$\delta = \frac{\sum \chi_i \delta_i}{\sum \chi_i} \qquad (3)$$

where χ_i is the mole fraction of protons of the i-th kind. Equation 3 can be rewritten as follows:

$$\delta = \frac{\delta^{\circ}\chi_o}{\sum \chi_i} + \frac{\sum^{s} \chi_i \delta_i}{\sum \chi_i} \tag{4}$$

where the first term gives the contribution from the hydrogenic positions of the solvent and $\sum^{s}$ means a sum over all exchangeable *substrate* protons. When the experiment is carried out in a very dilute solution, equation 4 simplifies to

$$\lim_{\chi_s \to 0} \delta = \delta^{\circ} + \frac{\sum^{s} \chi_i \delta_i}{\sum \chi_i} \tag{5}$$

Now, assume the same experiment is repeated in a mixture of light and heavy water of deuterium atom fraction n. Since the solution is diluted, the quantity $\sum \chi_i$ is almost equal to $(1 - n)$, the solvent protium mole fraction. Equation 5 can now be written as

$$\lim_{\chi_s \to 0} \delta = \delta_o + \frac{1}{(1 - n)} \sum^{s} \chi_i \delta_i \tag{6}$$

As was said before (*vide supra*), the *isotopic fractionation factor* for the i-th hydrogenic position in the solute should be expresses as follows:

$$\phi = \frac{\chi_i^D / \chi_i^H}{n/(1-n)} \tag{7}$$

The total mole fraction of hydrogens of the i-th kind is made up of the mole fraction of i-th type protia and the mole fraction of the equivalent deuteria. A quick mass balance reveals with the aid of equation 5 that the mole fraction of protia of the i-th type can be

expressed in terms of the total mole fraction of hydrogens of the i-th kind as follows:

$$\chi^{H}_{i} = \frac{(1 - n)\chi^{T}_{i}}{(1 - n + n\phi_{i})} \tag{8}$$

Recalling that the total mole fraction of hydrogens of the i-th kind equals the number of positions of the i-th type in the substrate molecule, (μ_i), times the substrate mole fraction, equation 6 can be written in its final form:

$$\lim_{\chi_s \to 0} \delta = \delta_o + \sum^{s} \frac{\mu_i \delta_i}{(1 - n + n\phi_i)} \chi_s \tag{9}$$

According to equation 9, for a very dilute solution, a plot of the observed chemical shift *vs* the substrate mole fraction should yield a straight line. When the experiment is carried out in pure protium oxide and also in a mixture of protium and deuterium oxides, the ratio of the experimentally determined slopes of the corresponding plots gives the following result:

$$\frac{\text{slope } (H_2O)}{\text{slope } (L_2O)} = \frac{\sum^{s} \mu_i \delta_i}{\sum^{s} \mu_i \delta_i / (1 - n + n\phi_i)} \tag{10}$$

We define as the overall isotopic *fractionation factor* of a particular substrate the number $\bar{\phi}$ such that:

$$\text{slope } (H_2O)/\text{slope } (L_2O) = 1 - n + n\bar{\phi} \tag{11}$$

Equation 11 will be used in this work to compute the overall fractionation factors of some substrates. This equation deserves a short comment. Since $\bar{\phi}$ is a sort of average fractionation factor, its use may not be completely free since erroneous conclusions might be

obtained. For example, straightforward conclusions can be drawn from the study of molecules containing only one exchangeable hydrogen or more than one of the same kind. Straightforward information can also be obtained from substrates with more than one exchangeable site in which no discrimination for protium or deuterium exists in most of the groups like in sugars (*vide infra*).

Statement of the Problem. Recent experimental[47-51] and theoretical[52-54] results have led to the proposal of selective cleavage of tetrahedral intermediates in ester and amide hydrolysis. This process seems to be controlled by *trans*-antiperiplanar oriented electronic lone pairs. *Gem*-diols and hemiketals (or hemiacetals) are good models for the tetrahedral intermediate in the solvolysis of esters, amides, and anhydrides. The purpose of this work is two-fold: first, to obtain the isotopic fractionation factor for *gem*-diols and hemiketals in an effort to accumulate this kind of indispensable data for the proton inventory method; and second, to contribute to the study of the structure of *gem*-diols.

RESULTS

In order to check the applicability and accuracy of the NMR method of measuring isotopic fractionation factors,[16-18] this quantity was determined for simple alcohols and in a mercaptane. The isotopic fractionation factors of these compounds had been previously determined by other methods.

TABLE IV-3. Isotopic Fractionation Factors for Simple Organic Compounds.

Compound	$\bar{\phi}$ (NMR)	$\bar{\phi}$ (Ref.)
Methanol	0.96 ± 0.05	1.0 (14,36,37)
Ethanol	1.05 ± 0.14	1.0 (14,35)
iso-Propanol	1.07 ± 0.30	1.0 (14)
tert-Butanol	0.97 ± 0.15	1.0 (14,18)
β-Mercaptopropionic Acid[a]	0.44 ± 0.02	0.43 (14,38)

[a]The fractionation factor of normal carboxylic acids has been found to be 1.00.

Reasonably good straignt lines were obtained in these experiments. Figure IV-1 shows the result for *iso*-propanol which is the experiment with the largest error.

The isotopic fractionation factors determined for some geminal hydroxylic compounds are given in Table IV-4.

FIGURE IV-1

DETERMINATION OF THE ISOTOPIC
FRACTIONATION FACTOR FOR *iso*-PROPANOL AT 301 K

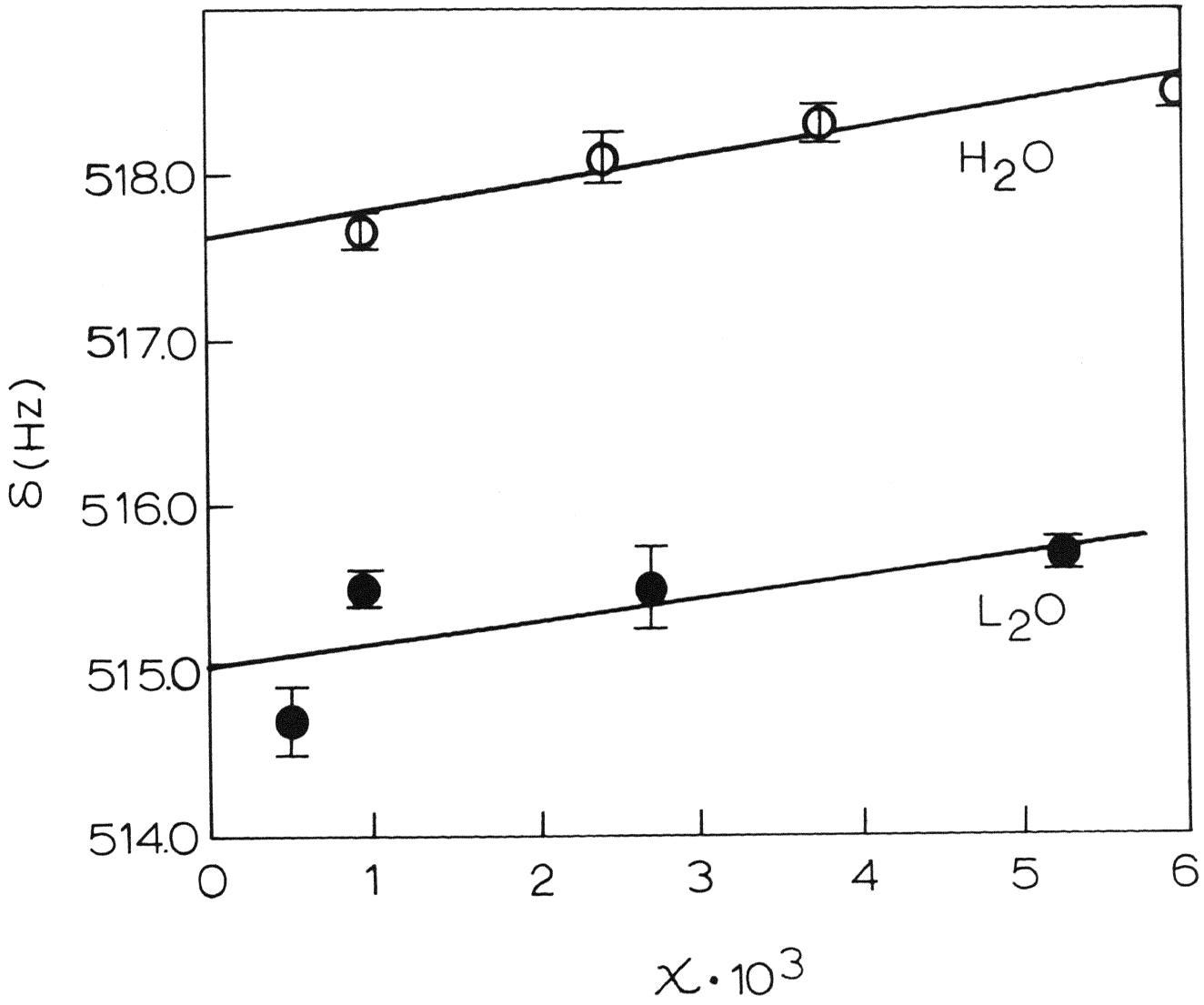

518.0
517.0
516.0
515.0
514.0
δ (Hz)
0
1
2
3
4
5
6
χ · 10³
H₂O
L₂O

TABLE IV-4. Isotopic Fractionation Factors for Geminal Hydroxylic Compounds.

Compound	$\bar{\phi}$
Chloral hydrate	1.23 ± 0.08
Ninhydrin	1.24 ± 0.20
D-Glucose	1.28 ± 0.17
D-Fructose[a]	1.23 ± 0.02

[a]D-Fructose in aqueous solution is 32% in the furanose form and 68% in the pyranose form [B. Andersen and H. Degn, *Acta Chem. Scand.*, 16, 215 (1962)].

The results given in this section indicate that hydrogens are more tightly bound in the hydroxylic positions of *gem*-diols, hemiacetals and hemiketals than in the corresponding site of simple alcohols and water.

DISCUSSION

The isotopic fractionation factors found for geminal hydroxylic compounds are of the order of 1.24 ± 0.04. Our findings agree with those given by Koizumi and Titani[31] for similar compounds (D-glucose, D-fructose and D-Mannose) in the temperature range 60-100°. The value of ϕ was found to be 1.15 ± 0.05. The same authors determined the fractionation factor of sucrose at room temperature and obtained a value of 1.21. Long and co-workers[32] calculated the fractionation factor of tetramethyl glucose to be 1.23.

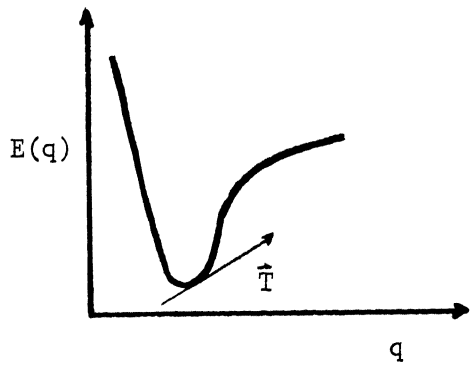
Equation 1 defines the isotopic fractionation factor as the kinetic isotope effect on the exchange process at the hydrogenic site of the substrate molecule, that is, $\phi = k_D/k_H$.

The fact that isotopic fractionation factors of geminal hydroxylic compounds (*gem*-diols, hemiacetals, hemiketals, etc.) is greater than 1 indicates that the binding potential of hydrogens in the hydroxylic positions of geminally substituted molecules is tighter than the binding potential of hydrogens in the same site of simple alcohols or water. The tightness of the binding potential is measured in terms of the curvature of the potential function itself. For the case of an anharmonic system, the curvature at the bottom of the well equals the magnitude of the corresponding force constant.*

---

*Let the potential function E = E(q) exist and $\vec{T}$ a tangent vector which defines the rate of change of the energy with the coordinate q.

Since there is a certain amount of double bond character in the carbon-oxygen bonds of *gem*-diols and molecules alike, it is logical to think that this torsional mode is hindered compared to the same motion in alcohols. Therefore, the torsional force constant must be greater for the case of *gem*-diols than for simple alcohols. To test the validity of this assumption, force constants for *gem*-diols were calculated from data in the literature for the torsional mode in methanediol[9] and hexfluoropropane-2,2-diol.[11] Table IV-5 gives these torsional force constants and that of methanol.[33]



One defines the curvature of E(q) as follows:

$$\text{curvature} = d\vec{T}/dS$$

where dS is the *arc element* along the curve. Applying the Pythagorian theorem to dS one obtains that the following relation occurs:

$$dS = \sqrt{1 + (dE/dq)^2}\ dq$$

The curvature at any point in E(q) is now given by

$$\text{curvature} = \frac{1}{\sqrt{1 + (dE/dq)^2}} \frac{d\hat{T}}{dq}$$

or the equivalent

$$\text{curvature} = \frac{1}{\sqrt{1 + (dE/dq)^2}} d^2E/dq^2$$

At the bottom of the well $dE/dq = 0$ and the curvature value equals the magnitude of the force constant of the particular mode

$$\lim_{q \to q_{eq}} (\text{curvature}) = \text{force constant.}$$

TABLE IV-5. Torsional Force Constants of Some Hydroxylic Molecules.

Molecule	f_θ (mdyne-Å/rad^2)
Methanol	0.011 (exp.)
Methanediol	0.192 (*Ab Initio*)
Hexafluoropropane-2,2-diol	0.074 (CNDO/2)

The molecular geometry in the *gem*-diols was that given in Figure IV-2[9,11] for perfluoro acetone hydrate.

The torsional force constant was also determined for protonated formaldehyde as a model for *gem*-diols by means of INDO calculations. The value of the energy of the system was obtained as a function of the HCOH dihedral or torsional angle as shown in Table IV-6 and Figure IV-3.

TABLE IV-6. Energy of Protonated Formaldehyde as a Function of the Torsional Angle Relative to the Minimum.

θ (degrees)	E (KJ/mol)
0.0	0.0
47.6	46.7
61.8	69.5
79.6	90.0
90.0	94.0

FIGURE IV-2

GEOMETRY OF THE *Gem*-DIOLS USED IN THE CALCULATIONS OF TORSIONAL FORCE CONSTANTS

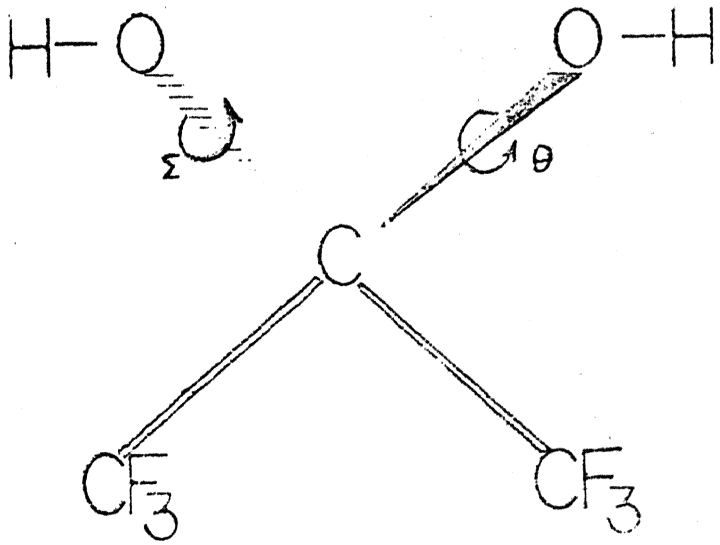
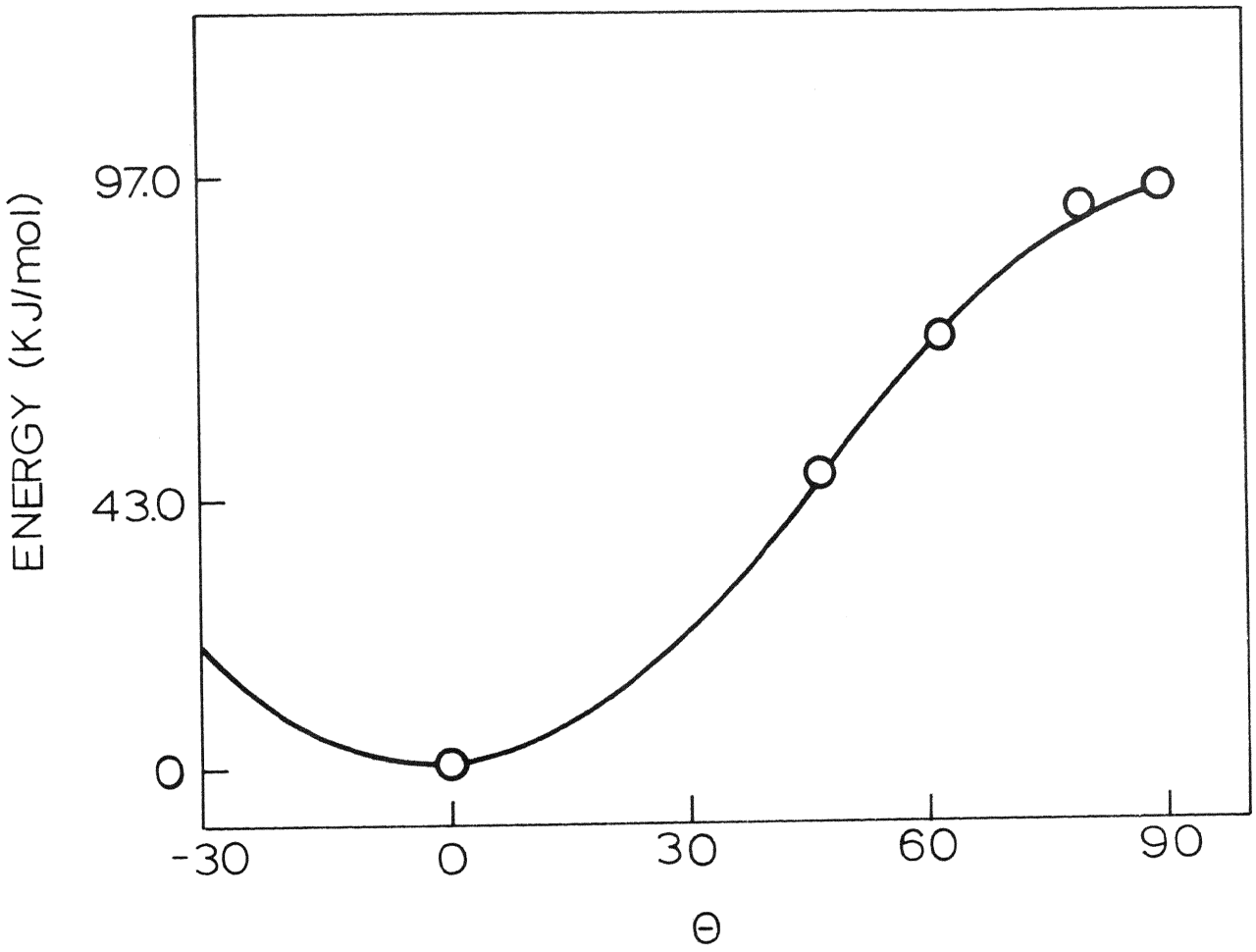

H
O
O
H
Σ
θ
C
CF3
CF3

FIGURE IV-3

ENERGY OF PROTONATED FORMALDEHYDE
AS A FUNCTION OF THE HCOH TORSIONAL ANGLE


ENERGY (KJ/mol)
97.0
43.0
0
-30
0
30
60
90
Θ

The torsional force constant was found to be equal to 0.31 mdyne-Å/rad^2, a value which is somewhat high due to the considerable double bond character left in the formaldehyde molecule after protonation.

The f_θ values obtained are certainly greater than the experimentally determined value for methanol indicating a stiffer rotor in *gem*-diols. With the values of f_θ obtained one can calculate theoretical values of isotope effects arising from isotopic substitution in the hydroxylic position of a *gem*-diol or similar compound.

Statistical mechanical calculations were performed on the following gas phase molecular system in order to obtain the equilibrium deuterium isotope effect:

$$CH_3\text{-}CHO + OL^- = CH_3\text{-}\underset{\displaystyle O_{(-)}}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}\text{-}H$$

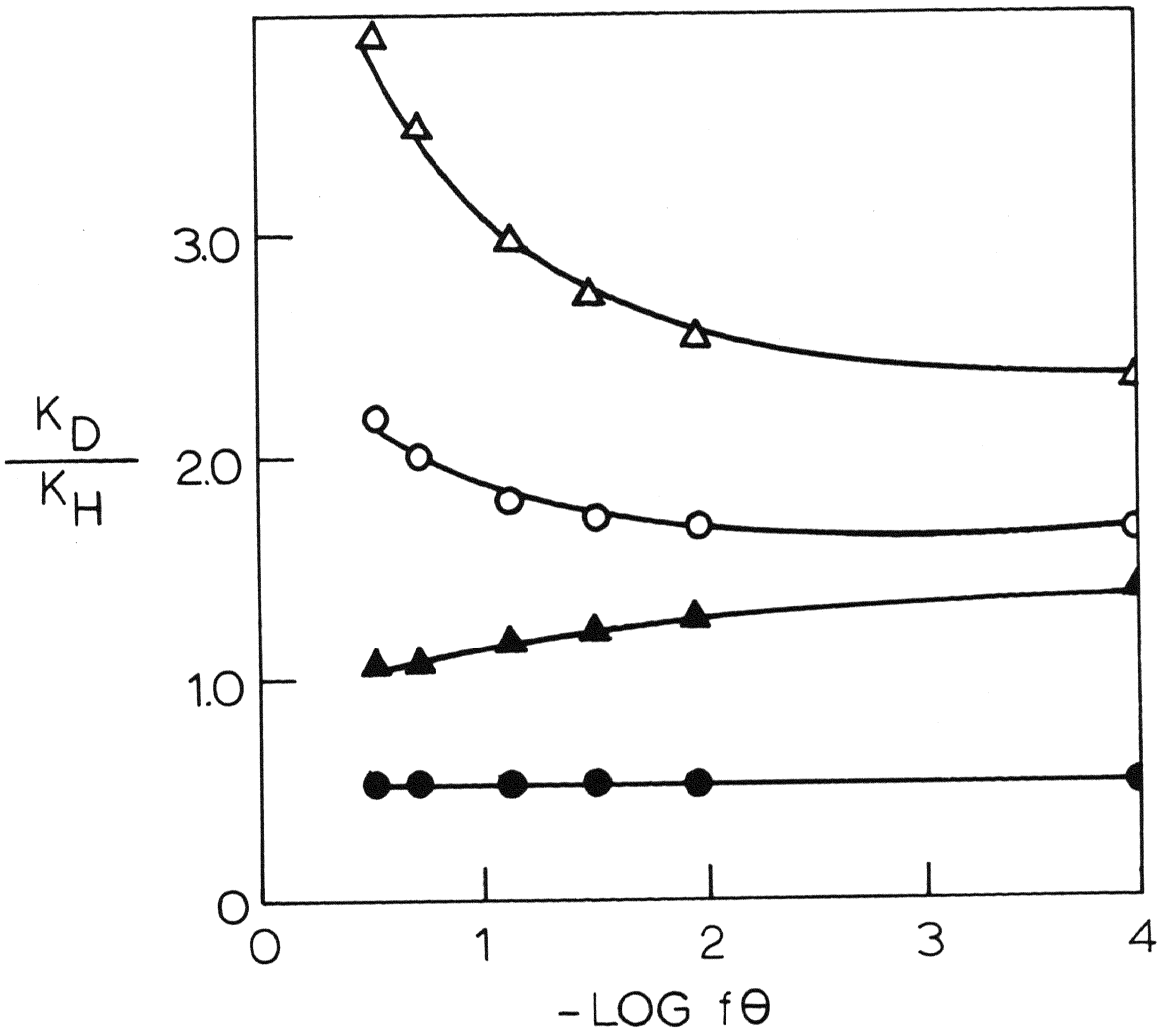
The C-OL torsional force constant was varied from 10^{-4} to 0.3 mdyne-Å/rad^2 and the results given in Table IV-7 and Figure IV-4.

TABLE IV-7. Calculated Equilibrium Deuterium Isotope Effect as a Function of the Hydroxylic Torsional Force Constant.

f_θ (mdyne-Å/rad^2)	MMI	EXC	ZPE	K_D/K_H
10^{-4}	0.5210	1.3874	2.3215	1.68
0.01	0.5210	1.2804	2.5430	1.69
0.03	0.5210	1.2175	2.7290	1.73
0.07	0.5210	1.1587	2.9820	1.80
0.20	0.5210	1.0940	3.4888	2.00
0.30	0.5210	1.0686	3.9000	2.17

FIGURE IV-4

EQUILIBRIUM DEUTERIUM ISOTOPE EFFECT
ON THE ADDITION OF HYDROXIDE TO ACETALDEHYDE AS A
FUNCTION OF THE HYDROXYLIC TORSIONAL FORCE CONSTANT


$\frac{K_D}{K_H}$
3.0
2.0
1.0
0
0
1
2
3
4
-LOG fθ

The table also gives the values of the MMI, EXC and ZPE terms. The MMI does not change since the molecular geometry was not changed in any calculation. The EXC and ZPE terms contribute in an opposite way to the overall isotope effect. This is better seen in Figure IV-4.

As the torsional force constant increases so does the K_D/K_H value, a result which is logical since the separation between the H and D levels becomes greater as the curvature of the potential well increases. The "torsional" equilibrium isotope effect, (K_D/K_H), can be defined as the ratio of the calculated isotope effect divided by 1.68 which is the isotope effect for "free" rotation. The values are given in Table IV-8.

TABLE IV-8. Torsional Isotope Effects as a Function of the Torsional Force Constant.

f_θ (mdyne-Å/rad^2)	$(K_D/K_H)_\tau$
10^{-4}	1.00
0.01	1.01
0.03	1.03
0.07	1.07
0.20	1.18
0.30	1.30

An empirical correlation can be obtained between the torsional isotope effect and the force constant in mdyne-Å/rad^2 as shown below.

$$(K_D/K_H)_\tau \cong 1 + f_\theta \qquad (12)$$

The significant result from these calculations is that inverse isotope effects can be generated from the hindrance of a torsional mode.

This last result confirms the non-classical molecular orbital picture of geminal diols and related molecules and simultaneously explains the inverse fractionation factors found experimentally in *gem*-diols and hemiketals.

The Appendix gives a list of calculated and observed fractionation factors for a wide variety of compounds.

EXPERIMENTAL

Determination of Isotopic Fractionation Factors by Nuclear Magnetic Resonance Spectrometry. (Notebook reference: Book II, pp. 14-16). A solvent mixture of about 95% deuterium atom fraction is recommended. The solute mole fraction is suggested to be within the range 0.001 to 0.01 in order to eliminate as much as possible errors due to uncertainty in finding the correct position of the signal and also to avoid problems due to non-ideal behavior of the solution such as specific solvent-solute interactions like protonation, etc., and solute-solute interactions like dimerization, etc.

All solutions were made gravimetrically for greater accuracy, being the isotopic mixture previously prepared by weighing out the necessary amounts of the isotopic components.

The observed chemical shift was recorded from the digital read-out of a Varian H.A. 100 using TMS (.5 mm coaxial cell) as an external reference. The temperature must be fixed at the desired value, though $\bar{\phi}$ must not be very sensitive to small changes in temperature. The observed shift must be an average of at least three readings reproducible to ±0.1 Hz. In order to obtain maximum accuracy the sample was in the probe at least 15 minutes before the readings were taken. The $\delta - X_s$ data were submitted to least squares analysis and $\bar{\phi}$ calculated as explained above (see equation 11). The uncertainty in the value of $\bar{\phi}$ was calculated as follows:

$$\% \text{ error in } \bar{\phi} \sim \sqrt{(\% \text{ error slope } H_2O)^2 + (\% \text{ error slope } L_2O)^2 + (\% \text{ error } n)^2}$$

Procedure for Calculating Force Constants. Energy profiles along the torsional dihedral exis were obtained from the literature for hexafluoropropane-2,2-diol[11] and for methanediol[9] at the specified molecular configurations (*vide supra*). These functions were fitted to a fourth order polynomion[21]

$$E = a_0 + a_1\theta + a_2\theta^2 + a_3\theta^3 + a_4\theta^4 \qquad (13)$$

except in the case of protonated formaldehyde in which it was possible to fit a sixth order polynomion. Ten points were fed to the polynomial regression program in each case. Table IV-9 gives the a_i values obtained for the two molecules mentioned above and for the results on protonated formaldehyde (*vide infra*).

The torsional force constants were obtained as the second derivatives of equation 13, evaluated at the equilibrium geometry.

Calculation of the Torsional Potential of Protonated Formaldehyde. These calculations were carried out by using the semi-empirical INDO self-consistent field molecular orbital method developed by Pople, Beveridge, and Dobosh.[22] The basic computer program used in these calculations was obtained from the Quantum Chemistry Program Exchange at Indiana University (QCPE 141). The program was modified in such a way that it can handle up to 150 basis orbitals, and matrix diagonalization was performed by using a modified Givens algorithm also available through the Quantum Chemistry Program Exchange (QCPE 62.3). All computations were preformed on the Honeywell 635 computer at the University of Kansas Computation Center. The computation time for each calculation was approximately 0.0015 hr. Five calculations were required to determine the torsional potential (*vide supra*).

TABLE IV-9. Coefficients for Equation 13.[a]

Compound	a_1	a_2	a_3	a_4	a_5	a_6	a_7
Methanediol	4.76364	-0.09160	-0.00120	0.00003	-0.00000	——	——
Hexafluoropropane-2,2-diol	1.77095	-0.02478	-0.00058	0.00001	-0.00000	——	——
Protonated Formaldehyde	0.53878	0.00000	0.00671	-0.00000	-0.00000	0.00000	0.00000

[a]Energies were given in Kcal/mol.

The basic geometry of protonated formaldehyde was obtained from Patrick A. Hogan of this group[23] and is given below:

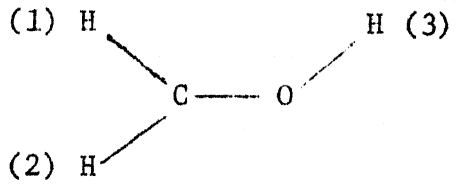


TABLE IV-10. Geometrical Parameters for Protonated Formaldehyde.

Bond	Length (Å)
C-H (1,2)	1.116
C-O	1.277
O-H (3)	1.05
Angle	**Value (°)**
HCH (1,2)	122.0
COH (3)	124.0

Maintaining the above variables constant, the H(1,2)-C-O-H(3) dihedral angle was varied from 0 to 90° and the value of the corresponding energies obtained.

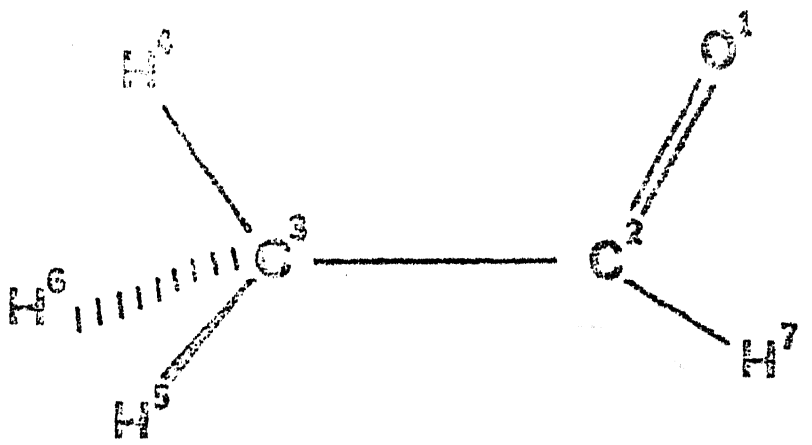
Computer Calculation of the Equilibrium Deuterium Isotope Effect in a Gem-Diol Model. The calculations were carried out by using a program provided to this group by Dr. Warren Buddenbaum, Department of Chemistry at Indiana University. The program is based on that of Schachtschneider

and Snyder[24] for the vibrational analysis problem and the program of Wolfsberg and Stern[25] for the calculation of isotope effects. The program can handle molecules of up to twelve atoms and thirty-six internal coördinates. More details on how the program works can be found in the instructions manual provided by Buddenbaum.[27]

The program was originally written for a Univac 1108 computer and was slightly modified by John L. Hogg[26] to run on the Honeywell 635 computer at the Computation Center of the University of Kansas. The geometries for the reactant and product states as well as the force fields were those used by Hogg[26] and are given in Tables IV-11, IV-12, IV-13, and IV-14.

Calculations were performed using the hydroxylic torsional force constant as the independent variable.

TABLE IV-11. Geometrical Parameters for Reactant Acetaldehyde Used in the Calculation of Theoretical Isotope Effects.

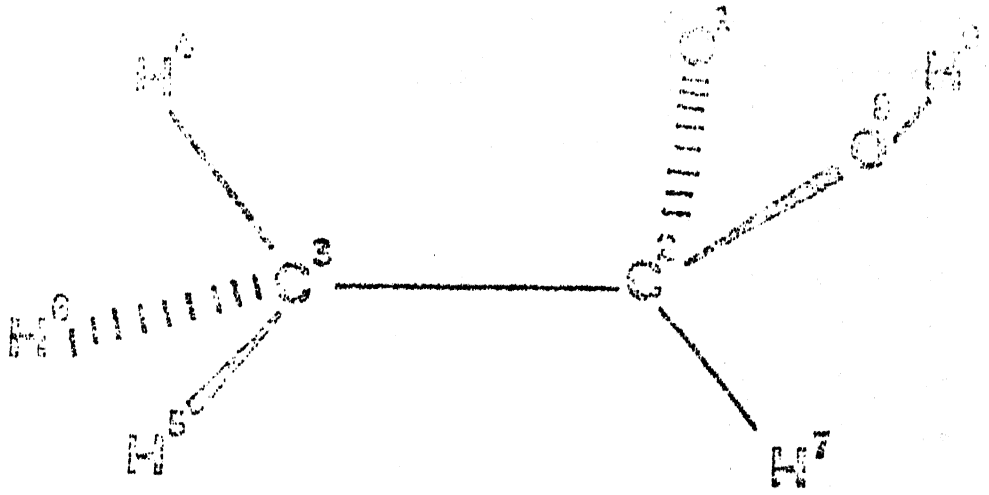


Bond	Length (Å)	Angle	Value (°)
C^2-H^7	1.114	$O^1-C^2-C^3$	123.9
C^2-O^1	1.2155	$C^2-C^3-H^4$	110.6*
C^2-C^3	1.5005	$C^2-C^3-H^5$	110.6*
C^3-H^4	1.086	$C^2-C^3-H^6$	110.6*
C^3-H^5	1.086	$C^3-C^2-H^7$	117.5
C^3-H^6	1.086		

Dihedral Angles	Value (°)
$O^1-C^2-C^3-H^4$	0
$O^1-C^2-C^3-H^5$	240
$O^1-C^2-C^3-H^6$	120
$H^4-C^3-C^2-H^7$	180

*Chosen to make H-C-H angles have value of 108.3° reported by Kilb, *et al.* [9]

TABLE IV-12 Geometrical Parameters for C^2-O^8 Bond Order of n = 1.0. This corresponds to the "product" structure.



Bond	Length (Å)	Angle	Value (°)
C^2-H^7	1.096	O^1-C^2-C^3	109.47
C^2-O^1	1.427	C^2-C^3-H^4	109.47
C^2-C^3	1.54	C^2-C^3-H^5	109.47
C^3-H^4	1.086	C^2-C^3-H^6	109.47
C^3-H^6	1.086	C^3-C^2-H^7	109.47
C^3-H^5	1.086	C^3-C^2-O^8	109.47
C^2-O^8	1.427	C^2-O^8-H^9	108.87
O^8-H^9	0.956		

Dihedral Angles	Value (°)
O^1-C^2-C^3-H^4	300
O^1-C^2-C^3-H^5	180
O^1-C^2-C^3-H^6	60
H^4-C^3-C^2-H^7	180
H^4-C^3-C^2-O^8	60
C^3-C^2-O^8-H^9	0

TABLE IV-13. Valence Force Constants for Acetaldehyde Reactants and Hydroxide Reactants.

Designation	Value*	Description
f_1	4.882	C^3-H^4 stretch
f_2	4.882	C^3-H^5 stretch
f_3	4.882	C^3-H^6 stretch
f_4	10.772	O^1-C^2 stretch
f_5	4.822	C^2-C^3 stretch
f_6	4.243	C^2-H^7 stretch
f_7	0.521	H^4-C^3-H^5 bend
f_8	0.521	H^4-C^3-H^6 bend
f_9	0.521	H^5-C^3-H^6 bend
f_{10}	0.432	C^2-C^3-H^5 bend
f_{11}	0.432	C^2-C^3-H^6 bend
f_{12}	0.432	C^2-C^3-H^4 bend
f_{13}	0.435	H^7-C^2-C^3 bend
f_{14}	1.006	O^1-C^2-C^3 bend
f_{15}	0.827	O^1-C^2-H^7 bend
f_{16}	0.296	C^2-H^7 bending against O^1-C^2-C^3 plane
f_{17}	0.009	O^1-C^2-C^3-H^4 torsion
f_{18}	0.009	O^1-C^2-C^3-H^5 torsion
f_{19}	0.009	O^1-C^2-C^3-H^6 torsion
f_{21}**	7.47	O^8-H^9 stretch

*Stretching constants in units of millidynes per angstrom. Binding constants in units of millidyne·angstrom per square radian.

**This was the only force constant used for the hydroxide reactants.

TABLE IV-14. Valence Force Constants for Various Transition States of C^2-O^8 Bond Order *n*.

Designation	Value of f	Description
f_1	5.13	C^3-H^4 stretch
f_2	5.13	C^3-H^5 stretch
f_3	5.13	C^3-H^6 stretch
f_4	7.877	O^1-C^2 stretch
f_5	4.3	C^2-C^3 stretch
f_6	4.4	C^2-H^7 stretch
f_7	0.521	H^4-C^3-H^5 bend
f_8	0.521	H^4-C^3-H^6 bend
f_9	0.521	H^5-C^3-H^6 bend
f_{10}	0.432	C^2-C^3-H^5 bend
f_{11}	0.432	C^2-C^3-H^6 bend
f_{12}	0.432	C^2-C^3-H^4 bend
f_{13}	0.5	H^7-C^2-C^3 bend
f_{14}	1.0	O^1-C^2-C^3 bend
f_{15}	0.8	O^1-C^2-H^7 bend
f_{16}	0.85	H^7-C^2-O^8 bend
f_{17}	0.005	O^1-C^2-C^3-H^4 torsion
f_{18}	0.005	O^1-C^2-C^3-H^5 torsion
f_{19}	0.005	O^1-C^2-C^3-H^6 torsion
f_{20}	5.35	C^2-O^8 stretch
f_{21}	7.62	O^8-H^9 stretch
f_{22}	0.77	C^2-O^8-H^9 bend
f_{23}	1.0	C^3-C^2-O^8 bend
f_{24}	2.0	O^1-C^2-O^8 bend
f_0	VARIABLE	O^1-C^2-O^8-H^9 torsion

*All units are the same as those reported in *TABLE IV-13.*

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APPENDIX I

ISOTOPIC FRACTIONATION FACTORS FOR HYDROGENS IN VARIOUS ENVIRONMENTS

Some fractionation factors were calculated by using the equation:

$$\phi = l^3 K_H / K_D$$

where l is the isotopic fractionation factor of hydronium ion and K_H and K_D the values of the acidity constant of the particular compound in protium and deuterium oxide at 298° K. The K_H/K_D values were taken from reference 42. The uncertainty of these values is probably ± 15% at the most, otherwise something else is indicated. Reference 43 gives tritium fractionation factors which were easily transformed into deuterium fractionation factors by means of the equation[41]

$$\log \phi_T = 1.44 \log \phi_D$$

The reader is advised to look in references 42 and 43 for more extensive tabulations of K_H/K_D and ϕ_T values.

a) *Fractionation Factors Obtained by NMR*

Hydroxylic Compounds

	ϕ	T (°C)	Reference
Methanol	0.96 ± 0.05	28	This work
Ethanol	1.05 ± 0.14	28	This work
iso-Propanol	1.07 ± 0.30	28	This work
tert-Butanol	0.97 ± 0.15	28	This work, see also 18
Chloral Hydrate	1.23 ± 0.08	28	This work
Ninhydrin	1.24 ± 0.20	28	This work
D-glucose	1.28 ± 0.17	28	This work
D-Fructose	1.23 ± 0.02	28	This work
β-Mercaptopropionic acid	0.44 ± 0.02	28	This work

Ions

Cyanide in methanol	1.00	28	45
Ethoxide in ethanol	0.72	RT	39
Hydrogen ion in water	0.69	RT	14
Hydrogen ion in methanol	0.62	RT	41
Hydroxide in water	0.50	RT	14
Methoxide in methanol	0.75	RT	40,41

b) *Fractionation Factors Obtained by Deuterium Exchange*

	ϕ	T (°C)	Reference
Methanol	1.00 ± 0.02	RT	36.37
Ethanol	1.09 ± 0.13	25	35
Benzoic Acid	1.07	RT	34
Phenol	1.08	RT	43
D-glucose	1.11	60-80	31
D-fructose	1.18	RT	31
Mannose	1.12	80	31
Sucrose	1.21	RT	31
Ethyl mercaptan	0.43	RT	38
Acetone, C-H	0.78	RT	38
Aniline	1.11	RT	34
Pyrrol	0.88	RT	34

c) *Fractionation Factors Obtained by Tritium Exchange*

Benzyl alcohol	1.10	RT	43
Pentaerythritol	0.95	RT	43
Benzoic acid	0.95	RT	43
p-Nitrobenzoic acid	0.92	RT	43
Acetanilide	0.91	RT	43
Acetophenone oxime	2.50	RT	43
Benzamide	1.17	RT	43
sym-Diphenylthiourea	0.96	RT	43

d) *Fractionation Factors Obtained from Acidity Constants in Light and Heavy Water*

Alcohols	ϕ	T (°C)	Reference
2-Chloroethanol	1.57	25	42
2,2,2-Trifluoroethanol	1.46	25	42
Enols			
2-Acetylcyclohexanone	1.06	25	42
2-Methyl pentanedione	0.82	25	42
Aliphatic Monocarboxylic Acids			
Formic	1.01	25	42
Acetic, h_3	1.06	25	42
Acetic, d_3	1.06	25	42
Pivalic	1.01	25	42
Fluoroacetic	0.84	25	42
Chloroacetic	0.90	25	42
Bromoacetic	1.01	25	42
Iodoacetic	0.86 (?)	25	42
Cyanoacetic	0.90	25	42
Phenylacetic	0.95	25	42
Half-Esters of Aliphatic Dicarboxylic Acids			
Monomethyl ester, tetramethyl succinate	1.04	25	42
Monomethyl ester, tetraethyl succinate	1.01	25	42
Butyl succinate	1.06	25	42

	ϕ	T (°C)	Reference
Monoethyl ester, malonate	0.92	25	42
Monoethyl ester, ethyl malonate	0.95	25	42
Monoethyl ester, diethyl malonate	0.88	25	42
Monoethyl ester, *iso*-propylmalonate	0.97	25	42
Monoethyl ester, maleate	0.95	25	42
Monoethyl ester, fumarate	0.97	25	42
Benzoic Acids			
Benzoic	1.00	25	42
o-Nitrobenzoic	0.88	25	42
m-Nitrobenzoic	1.04	25	42
o-Chlorobenzoic	0.97	25	42
Salicilic	1.34	25	42
1-Naphtoic	1.14	25	42
2-Naphtoic	1.01	25	42
Phenols			
Phenol	1.04	25	42
p-Bromophenol	1.28	25	42
m-Methoxyphenol	1.25	25	42
p-Methoxyphenol	1.34	25	42
o-Nitrophenol	1.25	25	42
p-Nitrophenol	1.25	25	42
4-Chloro-2,6-dinitrophenol	1.01	25	42
2-Naphtol	1.28	25	42
Phenyl ammonium ion	0.90	25	42

APPENDIX II

δ - X DATA

Separation of TMS and Hydroxyl Proton Resonances in Aqueous Solutions of Several Compounds.

The lines were fitted with program BIGRK. The δ values are averages of 4 consecutive readings.

a) *Chloral Hydrate*

H_2O		L_2O	
$X \cdot 10^3$	δ (Hz)	$X \cdot 10^3$	δ (Hz)
0.7	478.5	1.0	476.9
2.9	478.9	3.0	477.4
5.2	479.9	5.3	478.1
10.3	481.2	10.3	479.1

n = 0.957

slope (H_2O) = 288.7 ± 13.8

slope (L_2O) = 237.0 ± 10.9

b) *Ninhydrin* (#1)

H_2O		L_2O	
$X \cdot 10^3$	δ (Hz)	$X \cdot 10^3$	δ (Hz)
0.7	518.9	0.7	516.1
1.0	519.3	1.1	516.7
1.1	519.6	1.4	516.8
1.4	519.9	1.8	517.5

n = 0.935

slope (H_2O) = 1459 ± 121

slope (L_2O) = 1207 ± 123

c) *Ninhydrin* (#2)

H_2O		L_2O	
$X \cdot 10^3$	δ (Hz)	$X \cdot 10^3$	δ (Hz)
0.7	518.9	0.7	516.2
1.0	519.3	1.1	516.6
1.4	519.6	1.4	516.8
1.4	519.8	1.8	517.4

n = 0.935

slope (H_2O) = 1318 ± 156

slope (L_2O) = 1062 ± 82

d) *D-Glucose*

H_2O		L_2O	
$X \cdot 10^3$	δ (Hz)	$X \cdot 10^3$	δ (Hz)
0.7	520.5	1.1	517.5
2.2	521.5	2.2	517.8
4.1	522.0	4.2	518.2
8.3	525.1	8.4	520.9

n = 0.935

slope (H_2O) = 595.9 ± 44.9

slope (L_2O) = 472.4 ± 54.5

e) *D-Fructose*

H_2O		L_2O	
$X \cdot 10^3$	δ (Hz)	$X \cdot 10^3$	δ (Hz)
1.3	519.3	1.4	516.9
2.0	519.5	2.5	517.7
4.8	519.9	5.4	518.0
8.8	522.8	8.3	519.6
18.1	526.2	———	———

n = 0.933

slope (H_2O) = 426.8 ± 28.8

slope (D_2O) = 350.7 ± 51.3

f) *Methanol*

H_2O		L_2O	
$\chi \cdot 10^3$	δ (Hz)	$\chi \cdot 10^3$	δ (Hz)
1.99	519.3	0.9	517.6
6.06	519.8	1.8	517.7
9.26	520.1	6.5	518.2
———	———	9.3	518.5

n = 0.736

slope (H_2O) = 107 ± 4.1

slope (L_2O) = 111.1 ± 3.2

g) *Ethanol*

H_2O			
$\chi \cdot 10^3$	δ (Hz)	$\chi \cdot 10^3$	δ (Hz)
0.7	520.0	0.8	518.3
1.3	520.4	1.9	518.4
3.2	520.6	4.4	518.8
4.5	520.7	6.7	519.2
6.2	521.1	———	———

n = 0.736

slope (H_2O) = 162.9 ± 23.2

slope (L_2O) = 154.5 ± 8.0

h) *iso-Propanol*

$\chi \cdot 10^3$	δ (Hz)	$\chi \cdot 10^3$	δ (Hz)
0.9	517.6	0.5	514.7
2.4	518.1	1.0	515.5
3.8	518.3	2.8	515.6
6.0	518.6	5.3	515.8

n = 0.901

slope (H_2O) = 169.4 ± 19.0

slope (L_2O) = 158.6 ± 42.9

i) *tert-Butanol*

H_2O		L_2O	
$X \cdot 10^3$	δ (Hz)	$X \cdot 10^3$	δ (Hz)
0.8	519.7	0.8	516.8
1.9	519.3	1.9	517.0
2.7	519.7	3.8	517.8
3.9	520.4	8.7	518.4
7.7	520.6	———	———

n = 0.920

slope (H_2O) = 194.6 ± 29.9

slope (L_2O) = 200.4 ± 14.9

j) β-*Mercaptopropionic Acid*

H_2O		L_2O	
$X \cdot 10^3$	δ (Hz)	$X \cdot 10^3$	δ (Hz)
2.0	521.4	0.9	518.0
3.4	521.6	2.1	518.4
4.8	521.9	3.1	518.7
5.2	522.0	4.1	519.0
———	———	6.2	519.7

n' = 0.754

slope (H_2O) = 184.7 ± 9.4

slope (L_2O) = 321.7 ± 3.0

CHAPTER V

THE MECHANISM OF ION EXCHANGE IN CROSSLINKED CARBOXYLIC POLYMERS

Resin Structure and Properties. Many enzymes have metals built into their structures, require metals for activity or are further activated by metal ions.[1] Metal binding is obviously an important process in the chemistry of many enzymes. Direct mechanistic studies on metalloenzymes is a difficult task, since their structural details are not always known. Thus, we thought that it would be advantageous to turn to model systems whose chemistry could tell us something about their biological counterparts. Obviously, the model study had to be the transfer of a metal ion from an aqueous environment to a hydrophobic (or perhaps we should say "less aqueous") environment. As it is easy to realize, solvation changes on the metal ion are the key point. For example, association of simple alkali-metal salts is not observed in diluted aqueous solutions but proteins are able to bind them. This means that in the binding site, the protein is a better competitor than water. The chemistry of carboxylic ion exchange resins seems to offer the opportunity to study a model system for metalloenzymes. An advantage of this choice is that much is known about the structure of exchangers.[2] Since not much is known about the solvent isotope effects on the kinetics and equilibrium of enzyme-metal ion binding, one will not refer to the biological problem *per se* any further in this work*, because it would be too premature.

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*To our knowledge the only study on the SIE of a protein-ion binding process is that of Himes and Harmony (unpublished work, University of Kansas) in which the tetramerization of the protein formyltetrahydrosynthetase induced by Cs^+ was studied. The authors found an inverse KSIE of 4 and the proton inventory indicates the contribution from only one reactant-state proton.

There is an increasing interest in the chemistry of ion exchange resins, not only for their analytical applications but also because of their synthetic utility as catalysts.[3-5]

Ion exchange resins are commonly copolymers of "bridging units" and of "functional units." For example, the exchanger *Amberlite CG-50®* is a divinylbenzene-acrylic acid copolymer in which the divinylbenzene units provide tridimensionality to the polymeric matrix and the acrylic acid units perform the exchange process.

Detailed information about the nature and concentration of the exchange groups in the polymer can be obtained from potentiometric neutralization curves.[6] For example, Figure V-1 shows the titration curve of the carboxylic-acid type resin *Amberlite CG-50®*. The curve resembles that obtained in the neutralization of a weak monomeric acid. The gradual increase in the pH value at the equivalence point shows that the carboxyl groups are largely undissociated in acidic and weakly basic media. The pK_a value for this polymer is around 8, so the value for the change in the Gibbs function for the ionization of this polyacid is about +46 KJ/equivalent. In the case of the stronger exchanger *Amberlite IR-120®* [(poly) styrenesulfonic acid] the titration curve is given in Figure V-2 and the shape of the curve is typical of a strong monoacid. In this case, the pK_a value is near 3,5 which gives ΔG° = +21 KJ/equivalent. From these properties, one can conclude that the exchange of almost any cation for hydrogen ions must be a more spontaneous process for the sulfonic resin than for the carboxylic one, because in the latter the acidic hydrogens are still strongly bound to the carboxyl moiety.

Figure V-1

Titration Curve of *Amberlite CG-50*®

T = 298.16 K

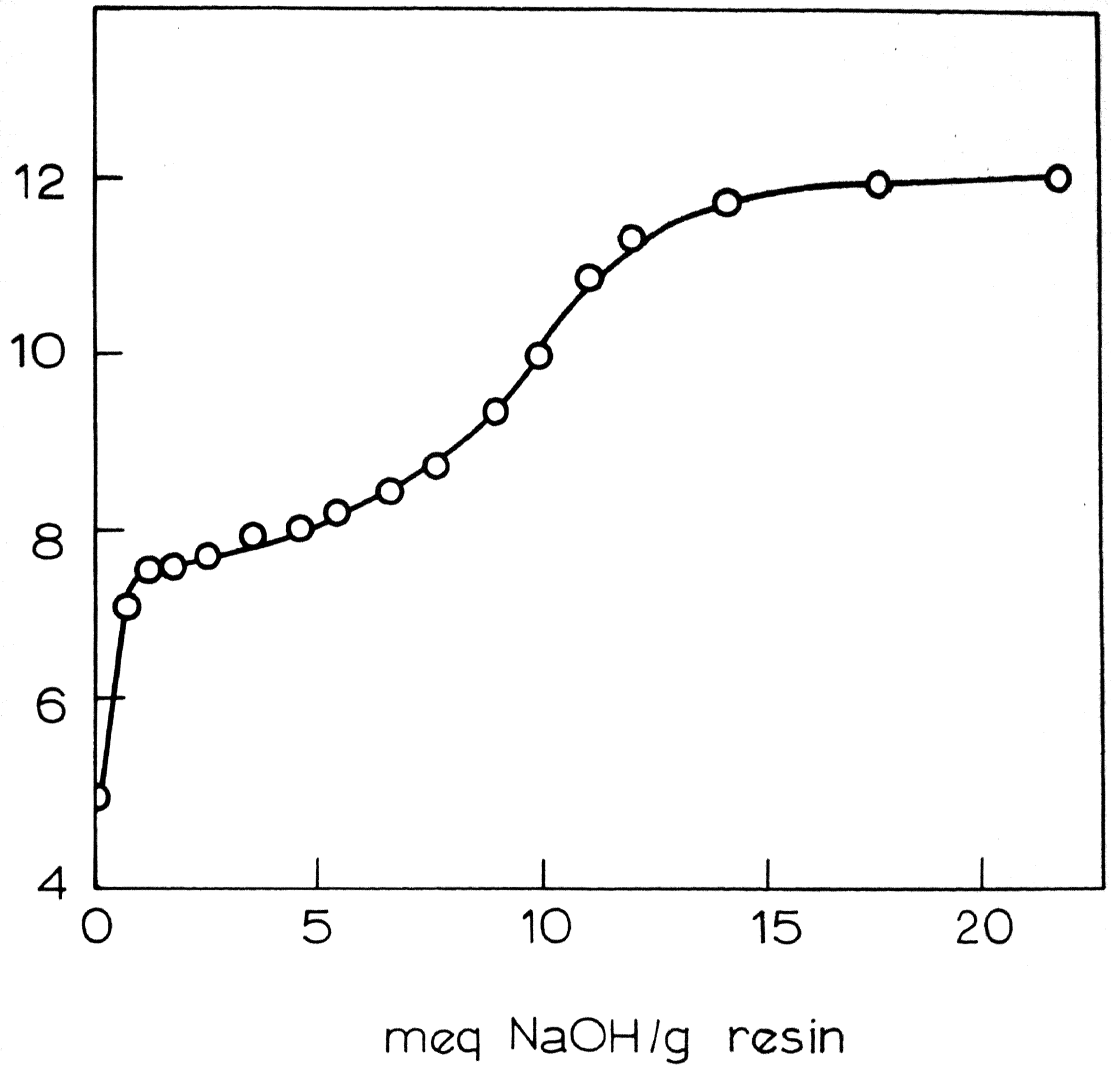
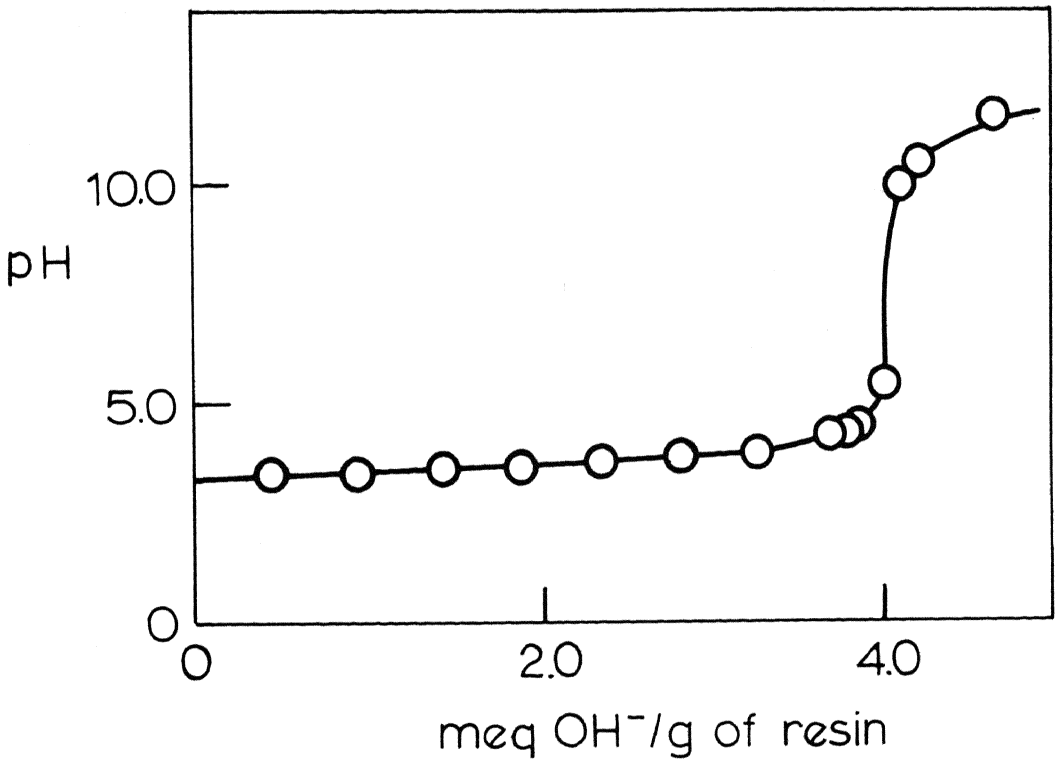

12
10
8
6
4
0
5
10
15
20
meq NaOH/g resin

Figure V-2

Titration Curve of *Amberlite IR-120*®

T = 298.16 K


10.0
pH
5.0
0
0
2.0
4.0
meq OH⁻/g of resin

Kinetics and Mechanism in Ion Exchange. The exchange mechanism can be said to consist of five main steps:

1) Mass transfer in the external solution up to the surface of the resin particle (film diffusion);

2) Diffusion inside the resin phase (particle diffusion);

3) Chemical exchange in the ionic groups;

4) Diffusion of the exchanged ion out of the interior of the exchanger;

5) Diffusion of the exchanged ion through the solution away from the resin particle.

As can be seen, the kinetics of the exchange process will be governed either by a diffusion or a mass action mechanism, although both driving forces reduce to the same thing: a gradient of chemical potential across the liquid phase-resin phase boundary (see Chapter II). Boyd, Adamson and Myers[7] give equations for the exchange process. Their results are based on a model in which the interactions between the ionic species are mainly coulombic in nature as in the case of strong-acid type resins. Since our experiments do not involve such a case, we shall not proceed any further in this discussion.

Statement of the Problem. A kinetic study will be made on the ion exchange process $Na(aq)^+$ + *Amberlite CG-50®* in order to obtain information on the exchange mechanism of carboxylic-acid type exchangers.

Results. The exchange reaction

$$M(aq)^+ + \textit{Amberlite CG-50®} \rightleftharpoons H(aq)^+ + \text{Resin salt}$$

was found to obey "first-order" kinetics. In neutral and slightly acidic

media the total extent of the reaction is about 3%. The rate of sodium exchange was determined at different ratios of outer metal ion concentrations (moles/l) to amount of resin (g). The results are shown below.

TABLE V-1. Specific Rate of Sodium Exchange*

$k_{Na} \cdot 10^3$ (sec^{-1})	$[Na^+]$/resin
7.32 ± 0.19	1.10
7.77 ± 0.08	1.41
6.93 ± 0.13	1.84
7.66 ± 0.07	2.00
7.41 ± 0.41	average

*All rates determined at 298.16° K and v_p/v_m = 1.17 (see text).

From the above results it can be learned that the transition state does not contain a sodium ion. The rate of the reaction was also measured under different hydrodynamic conditions. Since the experiments were conducted in a pH-Stat cell which has a motor-driven stirrer, the hydrodynamic parameter used here was the ratio of the propeller speed to motor shaft speed (for more details, see the experimental section), v_p/v_m. The following are the results obtained for sodium exchange.

TABLE V-2. Specific Rate of Sodium Exchange Under Different External Hydrodynamic Conditions.

$k_{Na} \cdot 10^3$ (sec^{-1})	v_p/v_m
7.41 ± 0.41	1.17
7.40 ± 0.54	2.06
7.41 ± 0.17	2.73

As can be seen, the external hydrodynamics does not perturb the reaction rate-determining step. To test whether or not there would be a change in the rate of exchange when different ions were used, experiments were performed on the rate of exchange of lithium, sodium and potassium. The results are shown below.

TABLE V-3. Rate and Kinetic Solvent Isotope Effect Values of Alkali-Metal Ion Exchange.

$M(aq)^+$	$k_M \cdot 10^3$ (sec^{-1})	k_{H_2O}/k_{D_2O}
Li	7.32 ± 0.19	———
Na	7.41 ± 0.41	3.06 ± 0.17
K	7.86 ± 0.22	3.31 ± 0.38

The nature of the cation seems not to have any effect on the rate of exchange. The proton inventory method was also applied to the elucidation

of the mechanism of this process and the results obtained are shown in Table V-4.

TABLE V-4. First-Order Rate Constants of Sodium Exchange in Mixtures of Protium and Deuterium Oxides.[a]

n	$k_n \cdot 10^3$ (sec^{-1})
0.0000	7.41 ± 0.41
0.1185	6.55 ± 0.18
0.2352	5.63 ± 0.12
0.3300	5.07 ± 0.08
0.4312	4.76 ± 0.05
0.5577	3.81 ± 0.23
0.6555	3.40 ± 0.05
0.7802	3.34 ± 0.20
0.9930	2.42 ± 0.04

[a] [NaCl] = 0.10 *M*.

Figure V-3 shows a plot with the above results. Since as a first approximation the reactant state species have unitary fractionation factors (H_2O and R-COOH),[8,9] the function k_n/k_o gives directly the transition state contribution to the solvent isotope effect. The line drawn through the points in Figure V-3 is the best cubic fit[11] (*vide infra*). Application of the F-test to the rate-n data gives the following result.

FIGURE V-3

First-Order Rate Constants of Sodium
Exchange in Mixtures of Protium and Deuterium Oxides

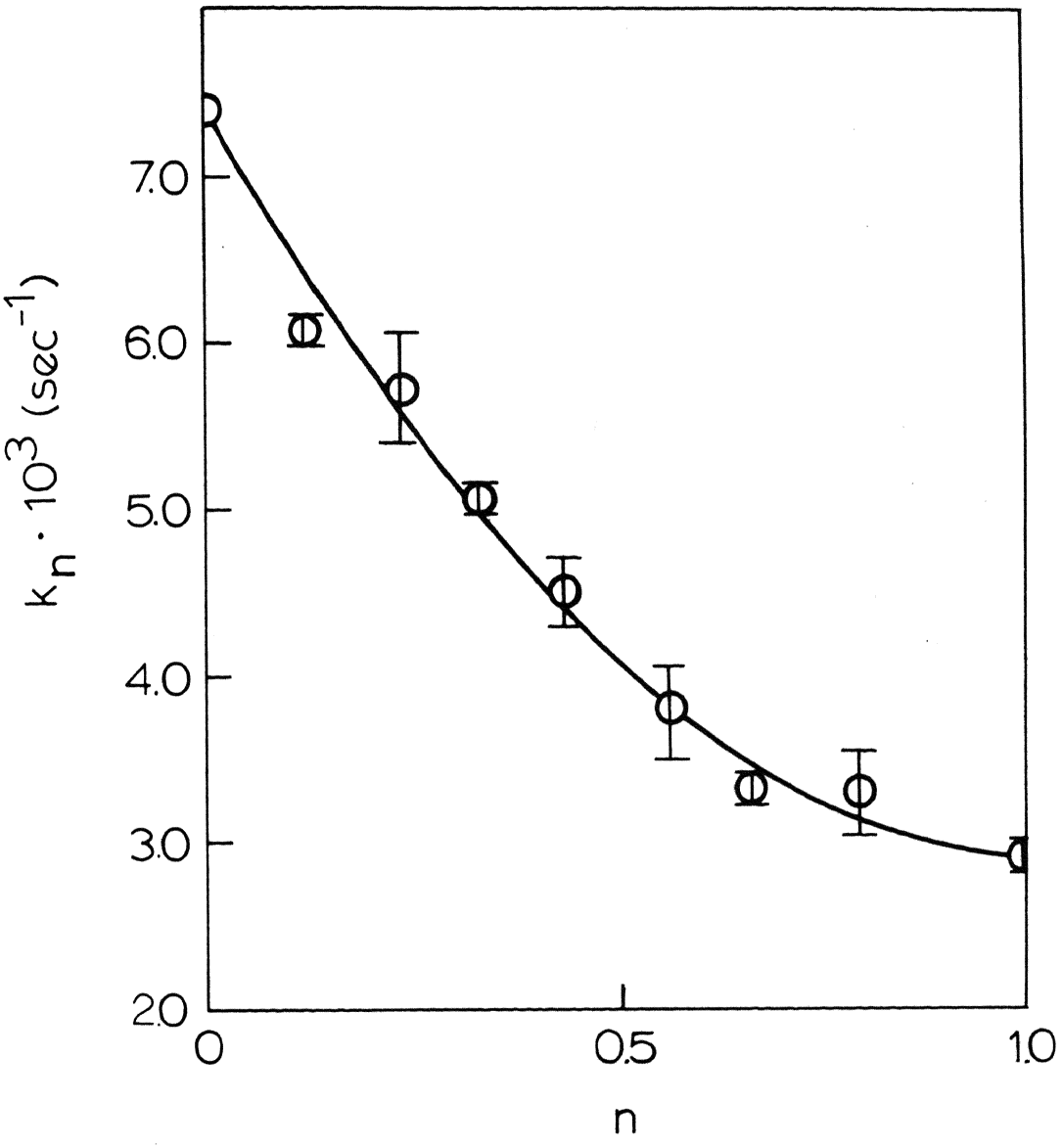

7.0
6.0
5.0
4.0
3.0
2.0
0
0.5
1.0
n
$k_n \cdot 10^3$ (sec^{-1})

TABLE V-5. Analysis of Variance for the Proton Inventory of Ion Exchange.[12]

	F-Value	F-Calc (%)
Linear Term	303	15 (99.9)
Quadratic Term	29	15 (99.9)
Cubic Term	0.6	1.8 (80)

According to the above analysis the cubic term is not significant at the 80% confidence level, although it is certain that this function is not a straight line at the 99.9% level. Since the rate data is not very precise ($\sim$ 3% error), the analysis of variance should be taken only as a guide to decide if this process involves the contribution from one or more than one proton.

DISCUSSION

Mechanistic Conclusions. To facilitate the discussion of the obtained results, the five main mechanistic steps which compose the exchange process will be listed again:

1) Mass transfer in the external solution up to the surface of the resin particle (film diffusion)

2) Diffusion inside the resin phase (particle diffusion)

3) Chemical exchange in the ionic groups

4) Diffusion of the exchanged ion out of the interior of the exchanger

5) Diffusion of the exchanged ion through the solution away from the resin particle.

The lack of dependence of the exchange rate on the external hydrodynamics indicates that film diffusion is not operative in the rate determining step. This result excludes steps 1 and 5 as being rate determining.

No dependence was found of the exchange rate constant on the nature of the metal ion, either. That is, diffusion of the metal ion through the polymeric matrix seems not to be the rate determining step. Moreover, the values of KSIE obtained are too large for a diffusion process, since the magnitude of KSIE for that kind of process should be roughly equal to the ratio of the diffusion coefficients of the diffusing particles in both isotopic media.[10]

Step 3 is highly unlikely to be rate determining due to the fact that it was shown that the transition state does not contain sodium. This analysis leaves diffusion of the newly formed hydronium ion through

the polymeric matrix as the only choice for the rate determining step. The magnitude of the KSIE (3.06 ± 0.17 for sodium and 3.31 ± 0.38 for potassium) suggests that a hydronium ion or an entity whose structure resembles closely that of a hydronium ion is involved in the rate determining step. The above assumption comes from the following argument. The fractionation factor for a $^{+}$O-H type of hydrogenic position is 0.69.[8] For the case of a hydronium ion being involved in the rate determining step, (with no contributions from the reactant state), the magnitude of the KSIE can be calculated as follows[8]:

$$k_{H_2O}/k_{D_2O} = 1/(0.69)^3$$
$$= 3.04$$

The result from the *proton inventory* experiments is not definite and in a case such as this, it should be considered as a good attempt to obtain more information. As shown in the section of results, the experiments indicate that at least two protons contribute to the observed KSIE. We think that three is a good possibility. Figure V-4 shows a plot of $\sqrt[3]{k_n/k_o}$ *vs* n. A straight line was obtained and from the slope the value of the fractionation factor obtained was ϕ = 0.70 ± 0.02. This last approach, although not analytically formal, is very logical, considering the rigorous validity of the previous results.

Kinetic Considerations. At this point, one thing remains to be explained: the first-order nature of the rate data. Figure V-5 shows a typical experiment (Na^{+} exchange in H_2O). One can see that the linearity of the plot is not optimum but nevertheless the points can be fitted to a straight line. Besides the fact that the measurements

Figure V-4

Cubic Root of the Ratio k_n/k_o
as a Function of the Solvent Isotopic Composition

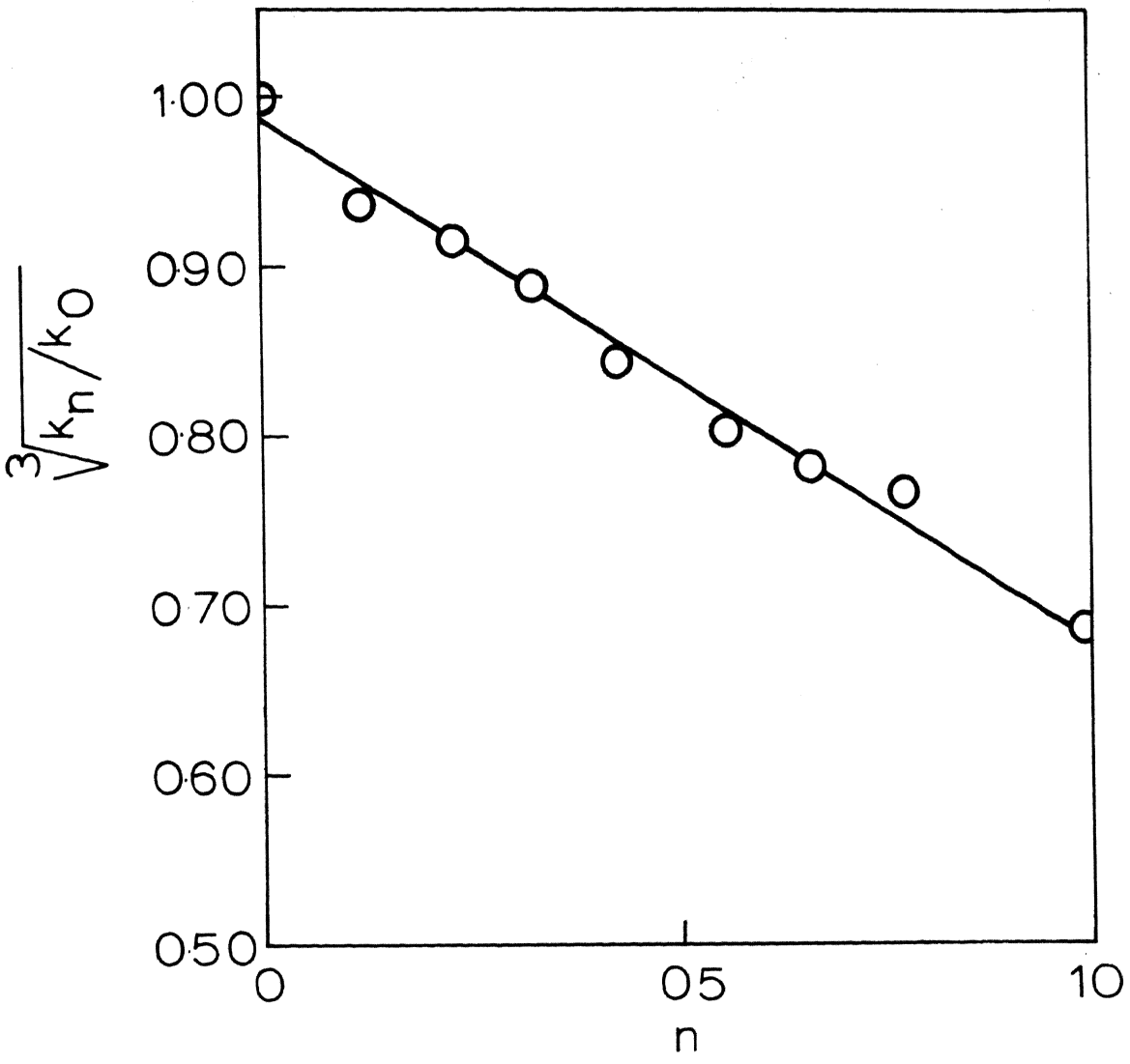
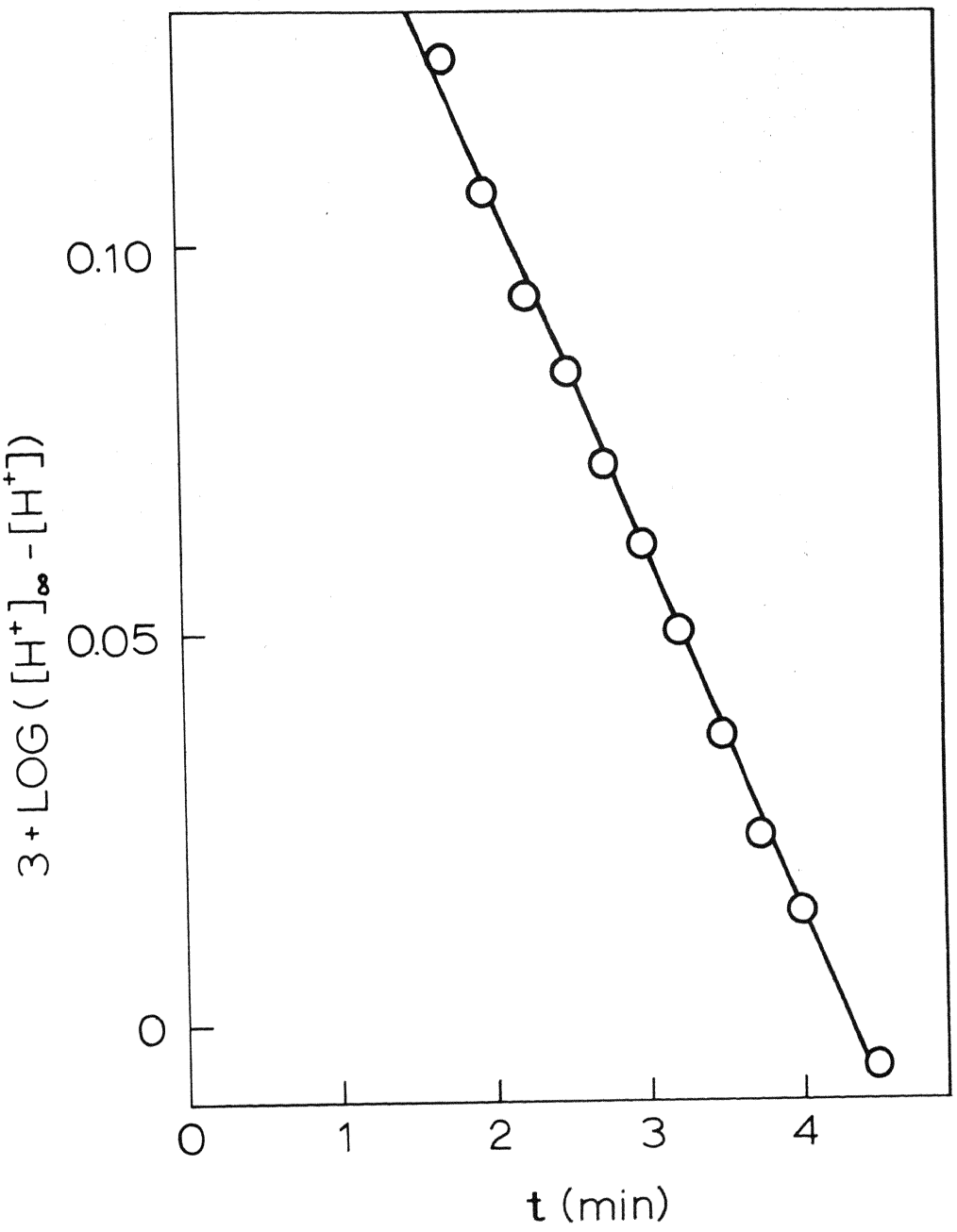

1·00
0·90
0·80
0·70
0·60
0·50
$\sqrt[3]{k_n/k_0}$
0
05
10
n

Figure V-5

Typical Exchange Experiment

Run #5 (see Appendix)


0.10
0.05
0
3 + LOG ([H+]∞ - [H+])
0
1
2
3
4
t (min)

are difficult to make, the heterogeneity of the system must be taken into account. The following is the kinetic scheme proposed to explain the results on the exchange process. Since there is a distribution of "local structures" in the resin phase, any property of the polymer is an average property. Let us have the exchange process at the i-th site in the polymer:

$$\sim\!\!\sim COOH \underset{}{\overset{K_i}{\rightleftharpoons}} \sim\!\!\sim COO^- \; H^+$$

$$\sim\!\!\sim COO^- \; H^+ \underset{k_i}{\overset{k_r}{\rightleftharpoons}} \sim\!\!\sim COO^- + H(aq)^+$$

$$\sim\!\!\sim COO^- + Na(aq)^+ \underset{k_e}{\overset{k_{-e}}{\rightleftharpoons}} \sim\!\!\sim COO^- \; Na^+$$

To simplify the matter, k_r, k_e and k_{-e} will be written as such in order to avoid having to write superscripts. The rate equations can be written primarily in terms of milliequivalents of species [( ) ≡ meq, c_i ≡ meq of H^+]. The fundamental equation gives the production of hydronium ion at the expense of the active sites. Hence, for the i-th site one has:

$$dc_i/dt = k_i(COO^- \; H^+)_i - k_r c_i (COO^-)_i \qquad (1)$$

By applying the steady-state approximation on $(COO^-)_i$ and by realizing that at any time $c_i = (COO^- Na^+)_i$, equation 1 can be written as follows:

$$dc_i/dt = k_i K_i (COOH)_i \left[1 - k_r c_i \frac{1 + k_{-e} c_i / k_i K_i (COOH)_i}{k_r c_i + k_e (Na^+)} \right] \qquad (2)$$

Equation 2 can be modified to yield

$$dc_i/dt = k_i K_i (c_i^{\infty} - c_i) \left[1 - k_r c_i \frac{1 + k_{-e} c_i / k_i K_i (COOH)_i}{k_r c_i + k_e (Na^+)} \right] \qquad (3a)$$

$$dc_i/dt = k_i K_i (c_i^{\infty} - c_i)(1 - F_i) \qquad (3b)$$

The significance of F_i is obvious from equation 3a. Since the extent of the reaction was found to be only a few per cent ($\sim$ 3%), as a first approximation one can consider F_i to be small compared to 1 and thus one obtains a first order decay for the exchange process at the i-th site in the polymer. The overall reaction rate is given by:

$$\sum^{\infty} dc_i/dt = \sum^{\infty} k_i K_i (c_i^{\infty} - c) \qquad (4)$$

or

$$d[H^+]/dt = \sum^{\infty} 1/V_T \, dc_i/dt = \sum^{\infty} k_i K_i ([H^+]_i^{\infty} - [H^+]_i) \qquad (5)$$

where V_T is the total volume of the system. The above equation can be integrated to give:

$$[H^+] = \sum^{\infty} [H^+]_i (1 - e^{-k_i K_i t}) \qquad (6)$$

As shown above, the exact form of the rate equation is complicated, but is essentially a sum of first-order terms. The observed rate data is therefore an average which could be thought of as follows:

$$\text{average rate} = \lim_{N \to \infty} \frac{1}{N} \sum^{N} \frac{d}{dt} (c_i / V_T) \qquad (7)$$

It is possible to define the observed rate constant in terms of the average diffusion rate constant and the average dissociation constant of the active groups in the polymer:

$$k_{obs} = \bar{k}_i \bar{K}_a \tag{8}$$

Since the average pK_a of the polymer was found to be about 8, the average value of k_i is of the order of 7×10^5 $M^{-1}sec^{-1}$, which is low compared to diffusion-controlled proton transfer in aqueous solutions (10^{10} $M^{-1}sec^{-1}$)[10]. This difference can be partially explained in terms of the so-called *obstruction effect*. In a solution of large particles (obstructions), these particles effectively block part of the diffusion area and therefore decrease the mobility of a small diffusing species. For example, Pikal, *et al.*,[13] have found that in mixtures of water and tertiary butyl alcohol, this last cosolvent lowers the mobility of protons. The authors observed that the miximum effect was obtained when there was a maximum build-up of water structure. They proposed that proton transfer is likely to operate between solvating water clusters and monomers, that is, protons jump from clusters to "high energy" monomers. This approach leads to the conclusion that an increase in solvent structure decreases the rate of proton diffusion. Boyd has recently measured the diffusion coefficients of Na^+ and NMe_4^+ in sulfonic-acid type exchangers,[14] and found their mobilities to be lower than in the bulk solvent. The author explained this result in terms of the *obstruction effect*.

Thus, the low value of the diffusion rate constant of protons inside *Amberlite CG-50*® can be explained in terms of three main effects:

1) As was said previously, the obstruction effect plays an important role in this process

2) Due to the very close packing in the matrix, ion-ion and ion-dipole interactions must have an appreciable effect on the diffusion activation energy.

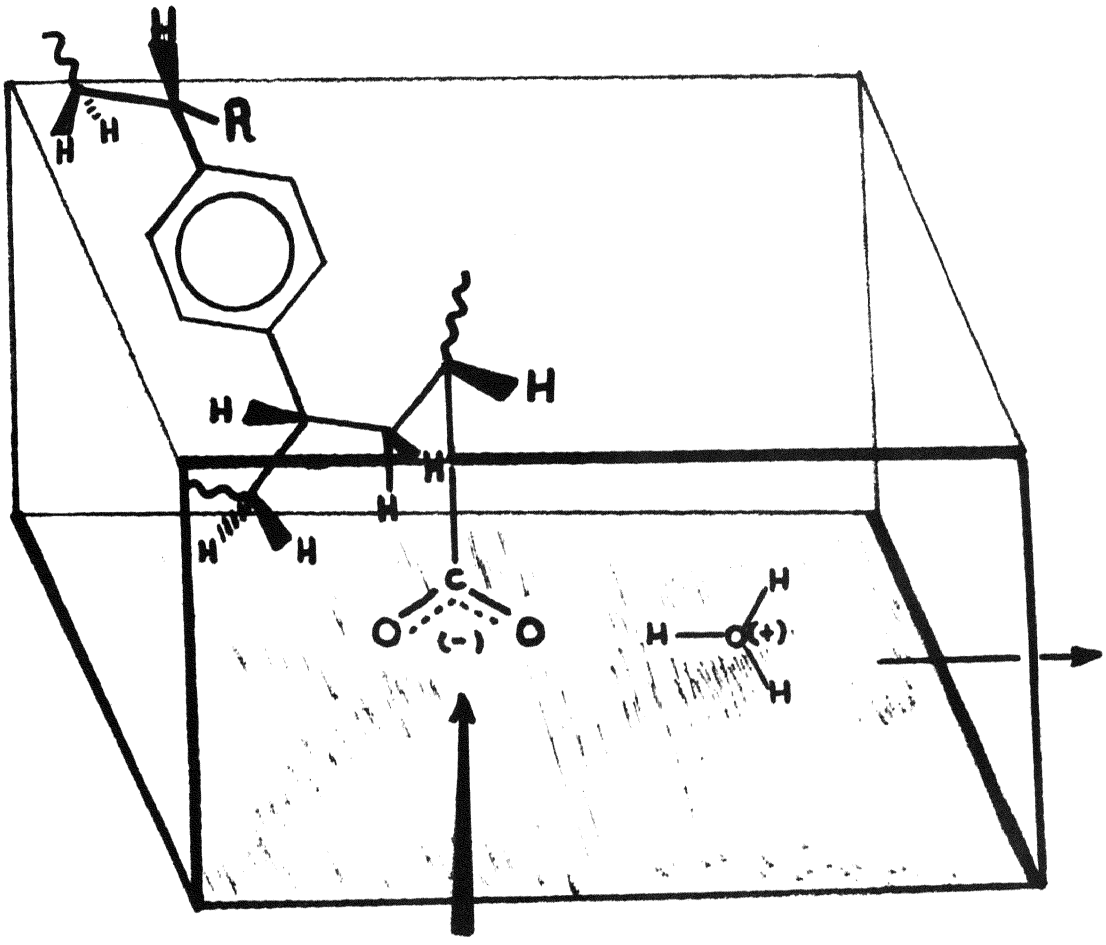
3) The very hydrophobic environment inside the matrix surely increases the structure of water in the resin phase thus decreasing the mobility of protons.

To finish this account, two main conclusions can be put forward: the first is that the exchange mechanism of carboxylic-acid type resins involves as the rate determining step the diffusion of the newly-formed hydronium ion through the polymeric matrix. Secondly, the mechanism in carboxylic polymers is different from that found in sulfonic-acid type polymers, in which diffusion of the metal ion through the matrix is the rate determining step, under the conditions described in this work.[7]

Figure V-6 shows diagramatically the proposed mechanism of the exchange reaction, in which the hydronium ion starts leaving and perhaps at the same time an "outer" metal ion enters in the matrix.

Figure V-6

Schematic Representation of
the Proposed Exchange Mechanism


R
H
H
H
H
H
H
H
H
C
O
(-)
O
H
O(+)
H
H
Na+

EXPERIMENTAL

Materials. *Amberlite IR-120®* from an unknown source and *Amberlite CG-50®* from Mallinckrodt were used as obtained. The metal chlorides were used without any further purification since they were analytical grade; lithium chloride obtained from Fisher Scientific Company, sodium chloride obtained from J. T. Baker Chemical Company, and potassium chloride from Mallinckrodt, Inc. Water was deionized tap distilled water. Deuterium oxide was purchased from Stohler Isotope Chemicals and was distilled before use.

Solutions. The solutions were made the same way reported in Chapter III.

Titrations. (Notebook reference: Book I, pp. 17, 24-5). Potentiometric titrations were essentially performed as suggested in reference 6. 0.1 g of resin and 10 ml of distilled water were placed in the thermally controlled cell of a Radiometer pH-Stat. From a 10 ml burette, small amounts of sodium hydroxide 0.1000 *N* were added and the pH of the solution recorded.

Kinetic Measurements. (Notebook reference: Book I, pp. 39-41) 0.2 grams of the dry resin was put in the pH-Stat cell which already contained 15 ml of the salt solution thermostated at 298.16K.The propeller was switched on and after about one minute the decrease of the "solution" pH was recorded at different time intervals. The early data (first minute, or around two minutes in heavy water) is not meaningful since many complex processes occur,namely exchange at the surface of the resin particle, swelling, etc. The pH-time data was converted to concentration-time data and first order plots constructed. Least-squares fitting was done on every set of data by using the computer program BGROK.

The stirring rate can be regulated by sliding the rubber belt which hooks the motor and the stirrer into the three different positions.

References

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(8) R. L. Schowen, "Mechanistic Deductions from Solvent Isotope Effects," *Prog. Phys. Org. Chem.*, 9, 275 (1972).

(9) See Chapter IV of this thesis.

(10) K. J. Laidler, "Chemical Kinetics," 2nd ed., McGraw-Hill Book Company, 1965, pp. 535-6.

(11) Polynomial regression using program BMD05R (version of August 16th, 1965), Health Sciences Computing Facilities, UCLA; obtained from the Computation Center, University of Kansas.

(12) R. A. Fisher and P. Yates, "Statistical Tables for Biological, Agricultural and Medical Research," 5th ed., Oliver and Boyd, London, 1957.

(13) J. A. Lanning, M. J. Pikal, and J. Q. Chambers, "The Effect of Water-Hydrocarbon Interactions on Proton Mobility. Chronoamperometric Diffusion Coefficients in Aqueous *tert*-Butyl Alcohol," *J. Phys. Chem.*, 78, 70 (1974).

(14) G. E. Boyd, "Mobility of Organic Cations in Cross-Linked Polyelectrolyte Gels. Measurements of the Self-Diffusion of Tetramethylammonium Ion," *J. Phys. Chem.*, 78, 735 (1974).

APPENDIX

Individual Rate Constants

exp. #	n	ion	v_p/v_m
1-4	0.000	Na^+	1.17
5-7	0.000	Na^+	2.06
8	0.000	Na^+	2.73
9-10	0.993	Na^+	1.17
11-13	0.000	K^+	1.17
14-15	0.993	K^+	1.17
16-17	0.118	Na^+	1.17
18-19	0.431	Na^+	1.17
20-21	0.656	Na^+	1.17
22	0.780	Na^+	1.17
23-24	0.235	Na^+	1.17
25-26	0.329	Na^+	1.17
27-29	0.558	Na^+	1.17
30-32	0.000	Li^+	1.17

C PROTON INVENTORY OF THE EXCHANGE REACTION:

$$NA(AQ)^{+} + AMBERLITE\ CG\text{-}50 == H(AQ)^{+} + AMBERLITE\ CG\text{-}50\text{-}NA$$

```
R=ERHSO?
Y
THIS PROGRAM IS DESIGNED TO DO A LINEAR LEAST SQUARES
ANALYSIS FOR DATA FITTING THE EQUATION FOR A STRAIGHT LINE.
THE PROGRAM HAS THE OPTION OF TAKING THE NATURAL LOGARITHM
OF THE DEPENDENT VARIABLE BEFORE THE FIT IS MADE.
DATA MAYBE ENTERED FROM THE PHOTOREADER OR THE TELETYPE.
 IF THE DATAARE READ FROM TAPE THE RUN NUMBER THEN THE NUMBER OF POINTS I
READ IN I4 FORMAT FOLLOWED BY THE X VALUES THEN THE Y VALUES IN 5F10.5 F
EACH DATA SET SHOULD BE FOLLOWED BY A RETURN AND LINE FEED AND THE
LETTER Y IF YOU WANT TO  MAKE MORE THAN ONE ANALYSIS.
 DO YOU WANT TO USE THE NATURAL LOG OPTION? DO YOU WANT TO USE THE
TELETYPE IO INPUT DATA?
YY
ENTER THE NUMBER OF THE RUN AND THE NUMBER OF POINTS
1 5
ENTER THE DATA POINTS IN SETS OF X THEN Y WITH ONE SET PER LINE
2.5 2.15
2.75 1.95
3.00 1.70
4.00 1.06
5.00 0.73


            RUN NUMBER    1


              SLOPE     -.4394E+00    STD. ERROR  .1144E-01 (-2.60%)
              INTERCEPT  .1857E+01    STD. ERROR  .4087E-01 ( 2.20%)

            RUN NUMBER    2


              SLOPE     -.4662E+00    STD. ERROR  .4928E-02 (-1.06%)
              INTERCEPT  .2251E+01    STD. ERROR  .1518E-01 (  .67%)


            RUN NUMBER    3


              SLOPE     -.4116E+00    STD. ERROR  .6517E-02 (-1.58%)
              INTERCEPT  .1868E+01    STD. ERROR  .2008E-01 ( 1.07%)


            RUN NUMBER    4


              SLOPE     -.4599E+00    STD. ERROR  .4064E-02 ( -.88%)
              INTERCEPT  .1824E+01    STD. ERROR  .1252E-01 (  .69%)


            RUN NUMBER    5


              SLOPE     -.4779E+00    STD. ERROR  .7866E-02 (-1.65%)
              INTERCEPT  .2041E+01    STD. ERROR  .2619E-01 ( 1.28%)
```

RUN NUMBER 6

SLOPE	-.4414E+00	STD. ERROR	.7369E-02 (-1.67%)
INTERCEPT	.1938E+01	STD. ERROR	.2454E-01 (1.27%)

RUN NUMBER 7

SLOPE	-.4136E+00	STD. ERROR	.9029E-02 (-2.18%)
INTERCEPT	.2043E+01	STD. ERROR	.3007E-01 (1.47%)

RUN NUMBER 8

SLOPE	-.4444E+00	STD. ERROR	.1005E-01 (-2.26%)
INTERCEPT	.1782E+01	STD. ERROR	.3348E-01 (1.88%)

RUN NUMBER 9

SLOPE	-.1470E+00	STD. ERROR	.3959E-02 (-2.69%)
INTERCEPT	.1548E+01	STD. ERROR	.3497E-01 (2.26%)

RUN NUMBER 10

SLOPE	-.1432E+00	STD. ERROR	.2076E-02 (-1.45%)
INTERCEPT	.1488E+01	STD. ERROR	.1805E-01 (1.21%)

RUN NUMBER 11

SLOPE	-.4875E+00	STD. ERROR	.5966E-02 (-1.22%)
INTERCEPT	.1583E+01	STD. ERROR	.1987E-01 (1.25%)

RUN NUMBER 12

SLOPE	-.4808E+00	STD. ERROR	.1567E-01 (-3.26%)
INTERCEPT	.1389E+01	STD. ERROR	.5192E-01 (3.74%)

RUN NUMBER 13

SLOPE	-.4458E+00	STD. ERROR	.7379E-02 (-1.66%)
INTERCEPT	.2342E+01	STD. ERROR	.2313E-01 (.99%)

RUN NUMBER 14

SLOPE	-.1352E+00	STD. ERROR	.1505E-02 (-1.11%)
INTERCEPT	.2176E+01	STD. ERROR	.1301E-01 (.60%)

RUN NUMBER 15

SLOPE	-.1480E+00	STD. ERROR	.2531E-02 (-1.71%)
INTERCEPT	.1962E+01	STD. ERROR	.2178E-01 (1.11%)

RUN NUMBER 16

SLOPE	-.3645E+00	STD. ERROR	.1206E-01 (-3.31%)
INTERCEPT	.1494E+01	STD. ERROR	.5306E-01 (3.55%)

RUN NUMBER 17

SLOPE	-.3646E+00	STD. ERROR	.1168E-01 (-3.20%)
INTERCEPT	.1893E+01	STD. ERROR	.5139E-01 (2.72%)

RUN NUMBER 18

SLOPE	-.2592E+00	STD. ERROR	.5714E-02 (-2.20%)
INTERCEPT	.1640E+01	STD. ERROR	.4189E-01 (2.55%)

RUN NUMBER 19

SLOPE	-.2797E+00	STD. ERROR	.3377E-02 (-1.21%)
INTERCEPT	.2037E+01	STD. ERROR	.2459E-01 (1.22%)

RUN NUMBER 20

SLOPE	-.1987E+00	STD. ERROR	.2826E-02 (-1.42%)
INTERCEPT	.2304E+01	STD. ERROR	.2375E-01 (1.03%)

RUN NUMBER 21

SLOPE	-.1999E+00	STD. ERROR	.5122E-02 (-2.56%)
INTERCEPT	.2478E+01	STD. ERROR	.4306E-01 (1.74%)

RUN NUMBER 22

SLOPE	-.2007E+00	STD. ERROR	.1189E-01 (-5.92%)
INTERCEPT	.9165E+00	STD. ERROR	.9146E-01 (9.98%)

RUN NUMBER 23

SLOPE	-.3531E+00	STD. ERROR	.9154E-02 (-2.59%)
INTERCEPT	.1457E+01	STD. ERROR	.3332E-01 (2.29%)

RUN NUMBER 24

SLOPE	-.3342E+00	STD. ERROR	.1473E-01 (-4.41%)
INTERCEPT	.1673E+01	STD. ERROR	.5361E-01 (3.21%)

RUN NUMBER 25

SLOPE	-.3087E+00	STD. ERROR	.1741E-01 (-5.64%)
INTERCEPT	.1239E+01	STD. ERROR	.7660E-01 (6.34%)

RUN NUMBER 26

SLOPE	-.2997E+00	STD. ERROR	.2672E-01 (-8.92%)
INTERCEPT	.1035E+01	STD. ERROR	.1111E+00 (11.05%)

RUN NUMBER 27

SLOPE	-.2148E+00	STD. ERROR	.1545E-01 (-7.19%)
INTERCEPT	.5877E+00	STD. ERROR	.7154E-01 (12.17%)

RUN NUMBER 28

SLOPE	-.2238E+00	STD. ERROR	.9753E-02 (-4.34%)
INTERCEPT	.6735E+00	STD. ERROR	.4845E-01 (7.20%)

RUN NUMBER 29

SLOPE	-.2419E+00	STD. ERROR	.1875E-01 (-7.75%)
INTERCEPT	.1187E+01	STD. ERROR	.9323E-01 (7.85%)

RUN NUMBER 30

SLOPE	-.3819E+00	STD. ERROR	.1622E-01 (-4.25%)
INTERCEPT	.8903E+00	STD. ERROR	.5732E-01 (6.44%)

RUN NUMBER 31

SLOPE	-.4424E+00	STD. ERROR	.1027E-01 (-2.32%)
INTERCEPT	.9091E+00	STD. ERROR	.3529E-01 (3.88%)

RUN NUMBER 32

SLOPE	-.4365E+00	STD. ERROR	.1123E-01 (-2.57%)
INTERCEPT	.7753E+00	STD. ERROR	.3860E-01 (4.98%)

CURRICULUM VITAE
March 12, 1975
Julio F. Mata-Segreda

Escuela de Química: 25-55-55
Universidad de Costa Rica
Ciudad universitaria "Rodrigo Facio"
San José, COSTA RICA

Apt. 178, San José
San José, COSTA RICA

Birth:	San José, Costa Rice August 3, 1948	
Marriage:	Victoria Eugenia Pacheco Secades January 9, 1972	
Children:	Julio Antonio July 28, 1972	
Education:	Liceo de San José, San José, COSTA RICA	1965
	Universidad de Costa Rica	1970 ("Bachillerato")
	Universidad de Costa Rica	1971 ("Licenciatura")
Positions:	Laboratory assistant(UCR)	1967
	Teaching assistant (UCR)	1968-71
	Teaching assistant (KU)	1972-73
	Research assistant (KU)	1973-75
Memberships:	Colegio de Químicos e Ingenieros Químicos de Costa Rica	
	American Chemical Society	
Meetings:	X Congress Latinoamericano de Química	1969
	Midwest Regional ACS Meeting	1973 (paper contributed)
	Midwest Regional ACS Meeting	1974 (paper contributed)